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# DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

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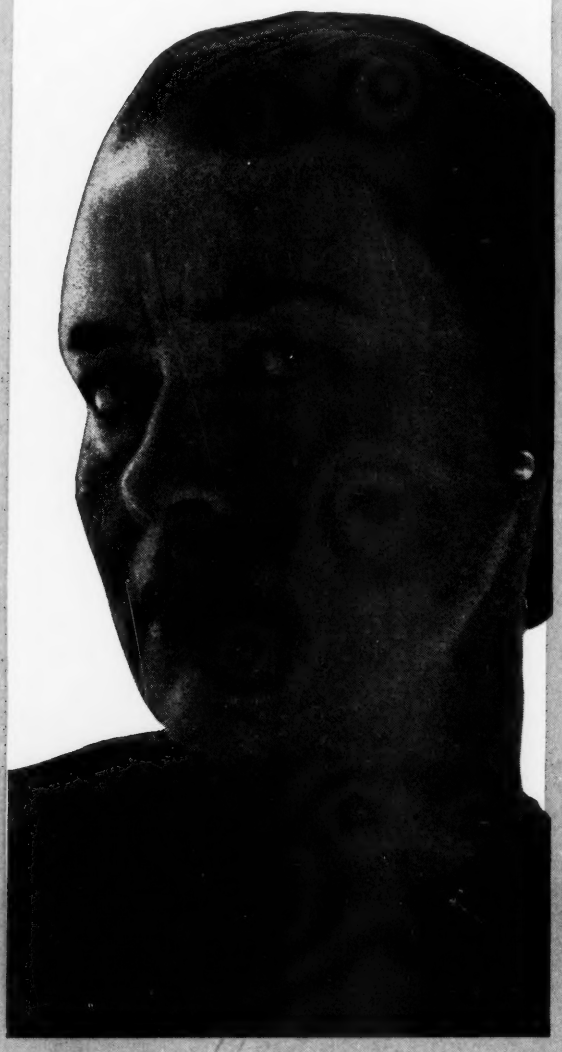

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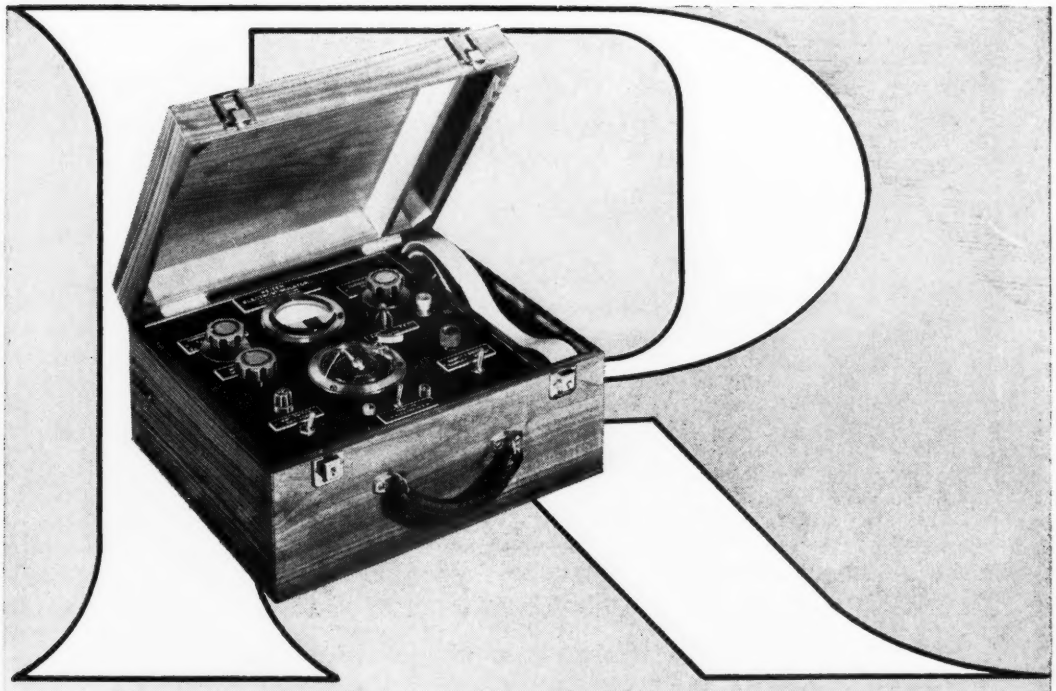

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DISEASES of the NERVOUS SYSTEM

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# Path for Projection of Non-Specific Diffuse Impulses to Cortex for EEG, Related to Consciousness

JAMES W. PAPEZ, M.D.
*Columbus, Ohio*

Nerve impulses of non-specific nature come from the reticular formation of the brain stem. They reach the intralaminar nuclei of the thalamus where they are relayed to the reticular nucleus and then to all parts of the cerebral cortex (Fig. 1). In the cortex they activate the EEG related to consciousness. This activation from the thalamus was demonstrated by Dempsey and Morrison.[2] Moruzzi and Magoun in 1949 found that the EEG was activated by impulses from the reticular formation of the brain stem.[11] A considerable amount of research has since demonstrated that the regions for activating the thalamic response extends from the reticular formation of the oblongata and pons through the tegmentam of the midbrain and the intralaminar and reticular nuclei of the thalamus.[1,3,4,6,7,10,21]

The purpose of this paper is 1) to indicate the paths which lead from the reticular formation and tegmental regions of the brain stem to the intralaminar nuclei of the thalamus, 2) to show the position of these nuclei and the organization of their fiber connections to the reticular nucleus and thence to the cortex, and 3) to suggest the connections they make in the cortex, presumably a substance related to EEG and consciousness.

*The reticular formation of the oblongata and pons* is a region entered by the fifth to twelfth cranial nerves (Fig. 1). The central connections of these nerves are integrated in this region for the performance of vital physiological functions such as respiration,[19] feeding, deglutition, cephalo-caudal control of visceral activities and of bodily muscles and their movements. In control of movement the vestibulo-spinal tracts and reticulo-spinal tracts play a leading part.[12]

One of the largest contributions to the reticular formation is the spino-bulbar tract. This is a lower link in the spino-thalamic path to the thalamus. From the bulbar region a reticular thalamic tract extends upward to the level of the thalamus. This tract was formerly described as central tegmental or dorsal trigemino-thalamic tract by older authors. Papez and others have pointed out that the tract

**Neural System for Consciousness**

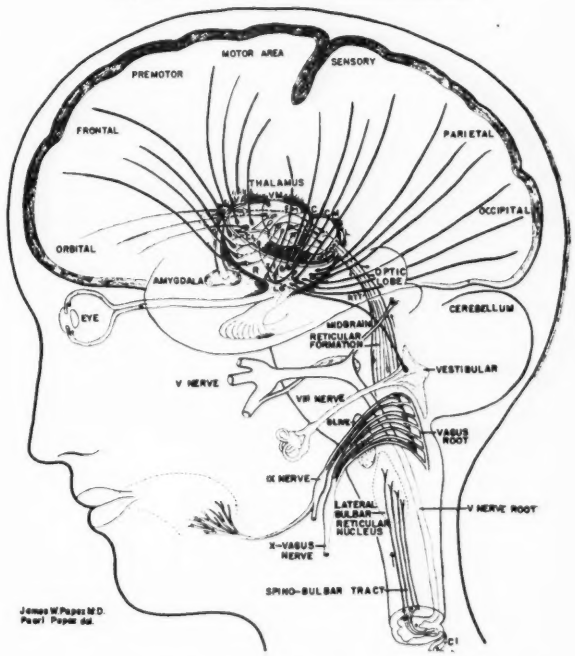


*Fig. 1.* Diagram of a non-specific path from the reticular formation of the brain stem, through the intralaminar and reticular nuclei of thalamus to all parts of the cerebral cortex without regard for specific areas. Its impulses produce EEG or alpha rhythms in the cortex related to consciousness.

Read before the Tenth Annual Meeting, Society of Biological Psychiatry, Chicago, June 11-12, 1955. Also at Harvard Medical School, Boston, May 2, 1955.

From Department of Mental Hygiene and Corrections, Ohio.

enters the centrum medianum and parafascicular nucleus in brains of lower mammals and man (Fig. 2, RTT). An impression has prevailed that this tract represented a visceral path to the submedial and ventral anterior nuclei of the thalamus thence to the basal frontal cortex. Its relation to EEG was then not known.

*The tegmental region of the midbrain* presents another tract of fine fibers mingled with the cells of the deep tegmental nucleus of the midbrain (Fig. 2, TGT). Accessions of fibers from central gray, from cell masses in the midbrain tegmentum, from the superior colliculus and collaterals from surrounding lemniscal systems enter the deep tegmental nucleus of the midbrain DT. Fibers arising in the deep tegmental nucleus pass to the subthalamic nucleus, posterior periventricular nucleus of the hypothalamus, and forward as tegmento-thalamic fibers TGT to the centrum medianum (Fig. 3, CM). Some continue into the intralaminar bundle (Fig. 4, I). From the foregoing list of connections and from experimental evidences it is evident that the deep tegmental nucleus DT is a subtectal region for integrating the various impulses into appropriate responses under the guidance of optic functions.[24] There are a number of reasons for inferring that afferent vagal-visceral functions pass forward in the tegmento-thalamic tract TGT to the submedial SM and ventral medical nuclei VM by way of the intralaminar bundle (Fig. 4, I). Presumably the inferior thalamic peduncle IP and anterior thalamic radiation AR complete this path to the oral and visceral areas of the cortex.

*The tecto-thalamic tract* (Fig. 2, TT) arises from the optic tectum but in man also from the region of the nucleus of the lateral lemniscus and parabigeminal nucleus. This tract runs up to contact the ventral pretectal nucleus PT beyond which it appears to enter the nucleus limitans (Fig. 3, L). This region of junction between the midbrain and thalamus has offered difficulties, and still presents uncertainties. The ventral pretectal nucleus (Fig. 2, PT) is a prominent structure in lower mammals and birds. It receives a large contingent of optic fibers. It sends fibers in two directions. One band passes to the peduncle of the substantia nigra under the red nucleus. Another band passes forward to the centrum medianum, to the nucleus limitans and internal medullary lamina of the thalamus (Fig. 3, L). There is here a diffuse thalamic connection. The suprageniculate nucleus has a similar obscure connection to the nucleus limitans L dorsal to it.[13,23]

There is a connection from the red nucleus to the centrum medianum.[16] The ventral part of the medial geniculate nucleus sends fibers to the centrum medianum a remnant of tractus tecto-reuniens seen in reptiles.[16]

The numerous fiber tracts sketched above bring a variety of impulses into the posterior intralaminar nuclei.[3,6,10] There is a definite organization in the posterior, middle and anterior intralaminar nuclei and their connections to the posterior, middle and anterior parts of the cerebral cortex.

**Midbrain Tegmentum**

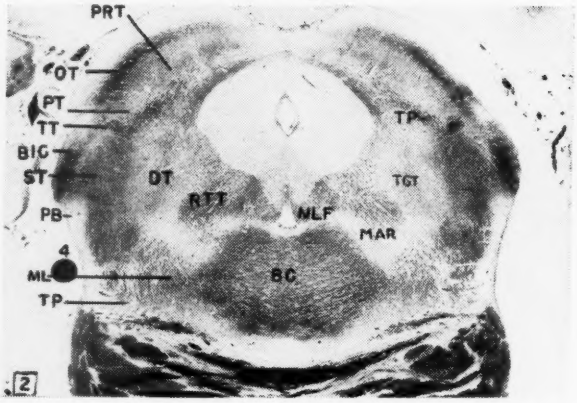


*Fig. 2.* Section through the midbrain of chimpanzee showing position of ascending reticular thalamic tract RTT, deep tegmental nucleus DT, and tecto-thalamic tract TT. Fine fibers in DT are tegmento-thalamic tract TGT. The main afferent tracts to the posterior intralaminar nuclei in figure 3. X6.

**Posterior Thalamus**

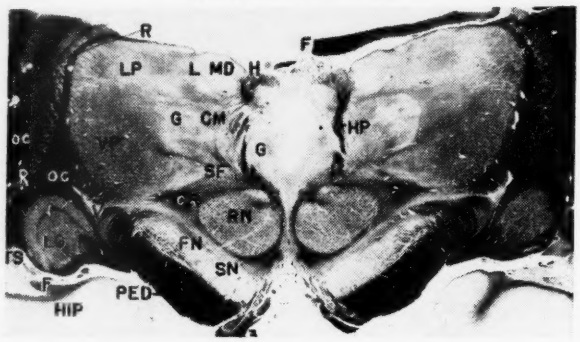


*Fig. 3.* Section through posterior thalamus of chimpanzee showing parafascicular nucleus PF, centrum medianum CM, and limitans nucleus L. They receive the tracts indicated in figure 2 above, and they send fibers to reticular nucleus R which sends non-specific fibers to occipital cortex along visual radiations. Note granule cell nuclei G. X4.

**Middle Thalamus**

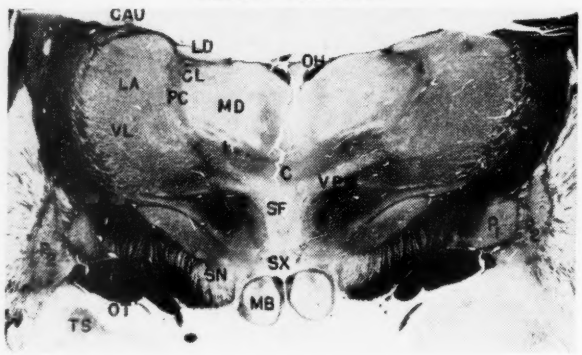


*Fig. 4.* Section near middle of thalamus through intralaminar bundle I, and central C, paracentral PC, and central lateral CL nuclei. Fibers from these nuclei pass ventrally and out to R, and also dorsally in lamina and out over LA to R. From reticular nucleus R fibers pass in internal capsule to temporal and parietal cortex. X4.

**Middle Thalamus**

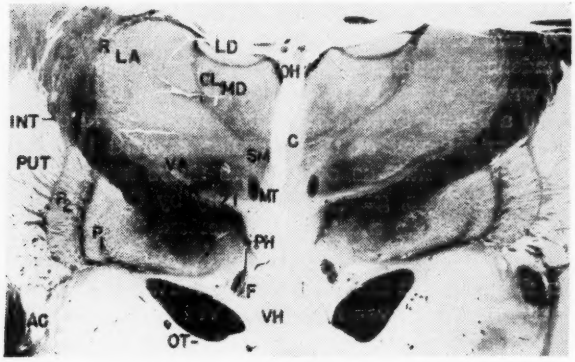


*Fig. 5.* Section through middle of thalamus showing submedial SM, central C, paracentral PC, and central lateral CL nuclei. SM gives origin to inferior thalamic peduncle IP. Connections from CL pass over LA to R and thence to posterior frontal cortex. X4.

**Anterior Thalamus**

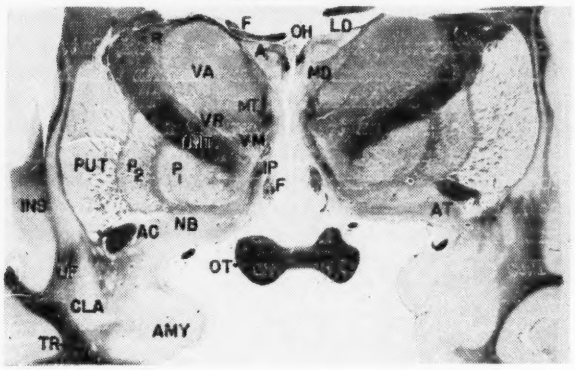


*Fig. 6.* Section through anterior thalamus and anterior perforated substance showing inferior thalamic peduncle IP entering the perforated substance and ending around nucleus basalis NB. Note amygdalar tract AT. X4.

**Anterior Thalamus**

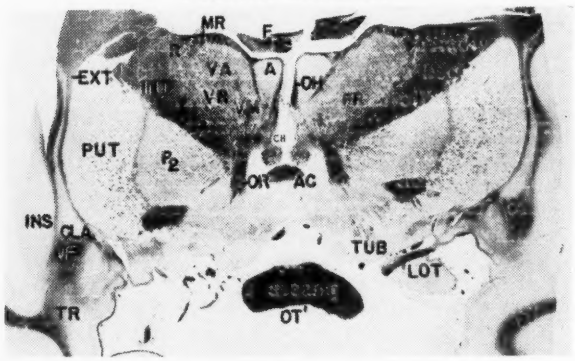


*Fig. 7.* Section through anterior nucleus A and anterior commissure AC showing the orbital radiation OR, ventral medial nucleus VM and frontal radiation FR to frontal polar cortex. X4.

| | |
|---|---|
| A | Anterior nucleus |
| AC | Anterior commissure |
| AMY | Amygdala |
| AN | Anterior tegmental nucleus |
| AT | Amygdalar tract |
| ATE | Anterior temporal nucleus |
| AP | Ansa peduncularis |
| BC | Brachium conjunctivum |
| BIC | Brachium of inferior colliculus |
| C | Central nucleus |
| Cau | Caudate nucleus |
| CC | Corpus callosum |
| CL | Central lateral nucleus |
| CLA | Claustrum |
| CM | Centrum medianum |
| CN | Cortico-nigral tract |
| CP | Cortico-pulvinar fibers |
| CR | Conjunctival radiation |
| DT | Deep tegmental nucleus |
| EXT | External capsule |
| F | Fornix |
| FN | Fronto-nigral tract |
| FP | Fronto-pontile tract |
| FR | Frontal radiation |
| G | Granule cell nuclei |
| H | Habenular nuclei |
| HIP | Hippocampus |
| HYP | Hypophysis cerebri |
| I | Intralaminar bundle |
| INS | Insula |
| INT | Internal capsule |
| IP | Inferior thalamic peduncle |
| IS | Interstitial spinal tract |
| L | Nucleus limitans |
| LA | Lateral anterior nucleus |
| LD | Lateral dorsal nucleus |
| LG | Lateral geniculate nucleus |
| LOT | Lateral olfactory tract |
| LP | Lateral posterior nucleus |
| MAR | Marginal nucleus of BC |
| MB | Mamillary body |
| MD | Medial dorsal nucleus |
| MG | Medial geniculate nucleus |
| ML | Medial lemniscus |
| MLF | Medial longitudinal fasciculus |
| MR | Medial cingulate radiation |
| MT | Mamillo-thalamic tract |
| NB | Nucleus basalis |
| OC | Occipital visual radiation |
| OH | Olfacto-, CH, cortico-habenular tracts |
| OLF | Olfactory bulb |
| OR | Orbital radiation |
| OT | Optic tract |
| P | Posterior commissure |
| $P_1$, $P_2$ | Inner and outer pallidum |
| PA | Paraventricular nucleus |
| PB | Parabigeminal nucleus |
| PC | Paracentral nucleus |
| PED | Cerebral peduncle |
| PF | Parafascicular nucleus |
| PH | Pallido-hypothalamic fibers ? |
| PR | Prerubral field |
| PRT | Tecto-pretectal tract |
| PT | Ventral pretectal nucleus |
| Pul | Pulvinar |
| Put | Putamen |
| R | Reticular nucleus of thalamus |
| RN | Red nucleus |
| RTT | Reticular thalamic tract |
| SF | Subfascicular nucleus |
| SG | Supragenicular nucleus |
| SM | Submedial nucleus |
| SN | Substantia nigra |
| SO | Supraoptic nucleus |
| ST | Spino-thalamic tract |
| SU | Subthalamic nucleus |
| SX | Subthalamic decussation |
| TGT | Tegmento-thalamic tract |
| TP | Tecto-pontile tract |
| TR | Temporal radiation |
| TS | Terminal stria |
| TT | Tecto-thalamic tract |
| TUB | Olfactory tubercle |
| UF | Uncinate fasciculus |

| | |
|---|---|
| VA | Ventral anterior nucleus |
| VG | Ventral geniculate nucleus |
| VH | Ventral hypothalamic nucleus |
| VL | Ventral lateral nucleus |
| VM | Ventral medial nucleus |
| VP | Ventral posterior nucleus |
| VPM | Ventral posterior medial nucleus |
| VR | Ventral thalamic radiation |
| VTT | Trigeminal thalamic tract |
| ZI | Zona incerta |

*The posterior intralaminar nuclei* (Fig. 3) are the parafascicular PF, centrum medianum CM and limitans L.[13,23] Two granule cell nuclei G are closely associated with them; stimulation of the medial one produces sleep.[5,15]

*The parafascicular nucleus* PF and *centrum medianum* CM receive ascending fibers from the reticular thalamic tract RTT. These fibers turn laterally and dorsally and break up into neurophil in the nuclei. Fibers of the tegmento-thalamic tract TGT enter the centrum medianum straight forward. Some continue farther into the intralaminar bundle (Fig. 4, I).

*The nucleus limitans* (Fig. 3, L) is situated lateral to the pretectal nuclei (labeled n.o.t. in 13). Large cells extend forward into the internal medullary lamina between the pulvinar and posterior end of the medial dorsal nucleus (Fig. 3, L). Nucleus limitans is embedded in the dorsal division of the brachium of the superior colliculus which may be efferent. It receives fibers from the tecto-thalamic tract TT. The suprageniculate nucleus is closely related to this system and possibly contributes fibers to the reticular nucleus.

The cells of the posterior intralaminar nuclei (Fig. 3, PF, CM and L) send their fibers laterally through the back surface of the pulvinar to terminate in the posterior end of the reticular nucleus R in proximity to the lateral geniculate nucleus LG. A conspicuous bundle from L is the dorsal division of the brachium of the superior colliculus. It is probably efferent ending in R. In general, the broad stratum of fibers which covers the posterior and dorsal surface of the thalamus (couche optique) is made up in large part of fibers from the intralaminar nuclei passing to the reticular nucleus R. The cells of the reticular nucleus send fibers into occipital visual radiation OC. This is a system of non-specific fibers whose impulses probably activate the occipital EEG or alpha rhythms. Observations indicate that it is a strongly developed and specially organized conduction pathway from the posterior intralaminar nuclei to the cortex of the occipital lobe. Stimulation of the granule cell area G medial to CM produces sleep.[5,15]

*The middle intralaminar nuclei* (Figs. 4 and 5) comprise the cells in the intralaminar bundle I, central nucleus C, paracentral PC, and central lateral CL nuclei in the internal medullary lamina. They begin posteriorly and extend anteriorly through the length of the thalamus, associated with posteriorly incoming fibers, and laterally fibers going out to the reticular nucleus R.

*The intralaminar bundle* (Fig. 4, I) arises from cells in the deep tegmental nucleus of the midbrain DT and centrum medianum CM. It appears as a condensed bundle of myelinated fibers as it passes forward. It includes cells of medium size which send a strong stream of fibers ventrally and out to the ventral part of the reticular nucleus R. This part of the nucleus contributes fibers into the internal capsules, going presumably by the temporal radiation TR to the temporal cortex.

The intralaminar bundle passes forward where its fibers end in the central C, paracentral PC, submedial SM, and ventral medial VM nuclei (Fig. 5).

*The central nucleus* C is close to the midline nuclei and extends into the massa intermedia. Fibers that pass through the massa intermedia come from the adjacent intralaminar nuclei and ascending periventricular fibers.[16] The fibers probably provide for a bilateral exchange of non-specific impulses. Granule cells and periventricular fibers are conspicuous features of this midline region. They may constitute an inhibitor mechanism.[15]

*The paracentral nucleus* PC is a broad, flat layer of cells in the internal medullary lamina which they occupy along a considerable extent. The cells send fibers in the lamina to the dorsally situated central lateral nucleus CL. Here the fibers join the common band which passes over the dorsal surface of the lateral anterior nucleus LA to end in the dorsal part of the reticular nucleus R.

*The central lateral nucleus* CL, at the upper border of the internal lamina lies under the lateral dorsal nucleus LD. Its fibers join the common band that goes over the dorsal surface to the reticular nucleus R. This in turn sends fibers into the internal capsule presumably going to the parietal and frontal cortex.

These nuclei in the middle of the thalamus form an obvious organization for supplying non-specific fibers to the temporal, parietal and posterior frontal cortex.

*The submedial nucleus* (Fig. 5 SM) is a large wedge-shaped cell mass bordered on its lateral side by the mamillo-thalamic tract MT. It receives a forward part of the intrathalamic bundle I. Presumably these are visceral afferent fibers coming from the region of the deep tegmental nucleus DT, where its connections from the central gray are prominent. The submedial nucleus gives rise to a conspicuous band, the *inferior thalamic peduncle* IP (Fig. 6). This passes forward, inclines ventrally and enters the anterior perforated substance to end around the nucleus basalis NB. The amygdalar tract AT continues to the amygdala AMY. The olfacto-habenular tract OH arises in the region of the nucleus basalis and goes to the habenula H. The foregoing connections may be regarded as a visceral afferent path to the olfactory reflex centers and amygdala. The motor outlet would be by way of the olfactory-habenular-interpeduncular-reticular-spinal pathway of ancient origin. This is suggested from comparative and experimental evi-

dences, visceral and feeding reactions have been demonstrated.[9]

*The medial dorsal nucleus* (Figs. 4 and 5, MD), where it borders the paracentral PC, presents a special band of fibers and cells. Fibers appear to join the inferior thalamic peduncle. Most fibers from the medial dorsal nucleus join the *frontal thalamic radiation* FR to the polar and inferior frontal cortex (Fig. 7). Some of its fine fibers also join the ventral radiation VR going to the pallidum.

*The ventral medial nucleus* (Fig. 7, VM) is situated in front of the submedial SM. It is closely allied to the front end of the ventral anterior VA. It receives fibers from the intralaminar bundle and gives rise to a conspicuous bundle, the *orbital radiation* OR. This passes ventrally across the anterior commissure through the striatum to the orbital cortex where visceral functions have been localized.[17]

*The ventral anterior nucleus* VA has a conspicuous connection to the frontal cortex. It shares this connection with the medial dorsal nucleus MD. The strong *frontal radiation* FR passes to the frontal medial, polar and inferior frontal gyri. Studies of lobotomies have shown the thalamic connections of this extensive cortex.[25] A part of the frontal radiation passes over the putamen and turns down in the external capsule to reach the claustrum and cortex of the insula. These regions were identified as visceral receptive areas by Penfield and Rasmussen.[17] They are closely related to the trigeminal, oral and vagal functions in the inferior frontal cortex. Origin of the fronto-pontile tract from this region was indicated by Yakovlev in studies of frontal lobotomies.[25]

*Anterior nucleus of the thalamus* A receives the mamillo-thalamic tract MT and gives rise to the medial cingulate radiation (Fig. 7, MR). The cingulate gyrus is the medial part of the visceral brain.[9] Its reactions are integrated by excitations from the hippocampal formation via the mamillary body MB.[9] They are related to consciousness. Stimulation of the surface of the cingulate gyrus supresses cortical activity.

*Zona incerta* (Fig. 5, ZI) is located in the frontal part of the ventral thalamus. It receives fibers from the ventral part of the lateral geniculate body and fibers from the pontile tegmentum coming up with the medial longitudinal bundle. It contributes fibers to the dorsal supraoptic decussation. Its main fiber connection is the *ventral thalamic peduncle* (Fig. 7, VP) which passes forward to end in the pallidum. In man it is a prominent triangular bundle which spreads over the medial border of the internal capsule.[16] The rest of the ventral thalamus has hypothalamic, subthalamic and rubral connections.

In review, it seems clear that the foregoing nuclei, SM, VM, VA and A and their radiations to the orbital, frontal, medial, inferior frontal and insular cortex constitute a frontal visceral mechanism dealing with integration of inner life, visceral and oral activities in a variety of ways.[18]

*Reticular nucleus* R is a shell of nerve cells that surrounds the dorsal thalamus on its lateral and anterior sides. It is a derivative of the original ventral thalamus. It receives fibers from the posterior, middle and anterior intralaminar nuclei.[3] There is a definite organization in the internal medullary lamina of nuclei and fiber connections projecting on the reticular nucleus, because each item can be identified. From its different parts, the reticular nucleus sends fibers into the internal capsule to all regions of the cortex, namely occipital, temporal, parietal, posterior frontal and anterior frontal (Fig. 1).

*Experimental studies* have demonstrated that the intralaminar nuclei of the thalamus and their connections project non-specific impulses to the reticular nucleus and beyond to all parts of the cortex where they evoke the EEG or alpha rhythms.[1,2,3,4,6,7,10] Moreover, these rhythms are correlated with the physiological state of consciousness,[20,22] a form of simultaneous facilitation.

*A mechanism for non-specific rhythms* appears to be present in the cortex as illustrated by Jasper.[6] The connections in the outer layers of the cortex deserve attention. Figure 8 shows on the left a non-specific fiber A from the reticular nucleus R, ending on a small pyramidal cell under layer *ii* by

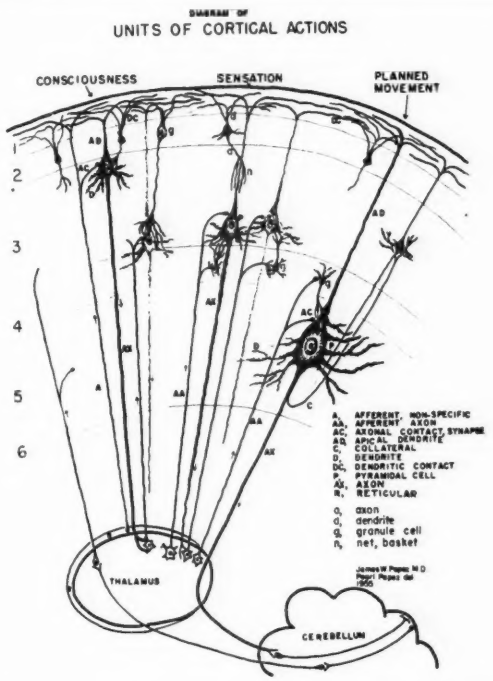


*Fig. 8.* Diagram of units of cortical action. At the left a non-specific fiber from reticular nucleus R ends in a synapse AC on a pyramidal cell P in layer *iiia* which fires an impulse back to thalamus along its axon AX. Its apical dendrite AD back-fires to dendrites of layer *i* where it makes contacts DC with dendrites of granule cells of layer *ii*. The granule cells discharge axons and terminal nets they form around pyramidal cells of layer *iiia*. This may be the field mechanism for EEG related to consciousness. At right similar units in deeper layers of cortex may mediate sensory and motor functions.

a direct axonal AC contact. The pyramidal cell by its axon fires down to the thalamus and excites a response in another thalamic cell. The apical dendrite of the pyramidal cell *back-fires* into layer *i* where it spreads to make dendritic contacts DC with dendrites of granule cells of layer *ii*. These granule cells discharge their axons into the nets which they form around the pyramidal cells. Stimulation of the surface of the cortex (and granule cells elsewhere) arrests or inhibits the functions of large conduction cells.[8,15,17,18]

*The substance of consciousness* presents special structural features in the cortex. The apical dendrites of pyramidal cells make contact with dendrites of granule cells of layer *ii*. This is a back-fire type of dendrite to dendrite contact which stimulates the granule cells when the pyramidal cell fires. It is a neurophil type of field arrangement of contacts that begins in the reptiles and prevails in mammals. This type of substance in action is probably responsible for consciousness. Consciousness is a self-possessed experience of the individual which makes possible mentation in self-possessed sensory, intersensory and action fields, as shown on the right side. It is an act of facilitation.

*Evolution of the intralaminar and reticular system* is seen in an early stage in brains of reptiles.[14] There the anterior and medial thalamic nuclei have forward connection to the basal parts of the forebrain including basal ganglia. A tecto-thalamic tract ends in these nuclei. A reticulo-thalamic tract ends in the nucleus reuniens, the homologue of the intralaminar nuclei. This extensive nucleus is connected directly to the old reticular nucleus which probably sends non-specific fibers to the cortex. There are no true posterior and lateral thalamic nuclei on the outside of the internal medullary lamina in reptiles. The cortex of reptiles has in places only the first layer of fibers and second layer of granule cells, especially in the fascia dentata. There are some scattered nerve cells above the genetic pendymal layer of neuroblasts. Reticulo-cortical fibers are few.

In summary a system of connections from the reticular and tegmental regions of the brain stem through the intralaminar and reticular nucleus of the thalamus and thence to the cortex has been traced in sections of human, chimpanzee, and macaque brains. Organization and fiber connections of these thalamic nuclei and their radiations to the cortex received special consideration. There was found a close correlation between this anatomical organization and physiological pathways traced by many recent investigators. The substance of conscious has thus been defined for this facilitation.

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# Prospects in Psychopharmacology

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Medications have been used for a long time for brain diseases, but now we are developing pharmacological agents that influence the mind as well. Against such a dichotomy between brain and mind we have the idea that any sharp delimitation between these two aspects of behavior is not possible; on the contrary we have a continuous spectrum. For example, though we prescribe atropine and atropine-like drugs against Parkinsonism and the new tranquillizing drugs to mitigate hallucinations and delusions, atropine does affect the mind and can even bring on an organic confusion while Parkinsonism is one of the side reactions of the new drugs. Therefore one term to include the entire gamut of such drugs would be preferable. The descriptive designation of neuropharmacology is acceptable. Yet on an operational basis, because some are more interested in the practice of neurology and others in psychiatry, it seemed advisable to use the name psychopharmacology to emphasize the new direction taken by pharmacology.

Pharmacological treatments for the mind are not new. They have been employed for a long time. In the past we have gradually developed methods to deal with disturbed, hallucinating and delusional patients. Barbiturates bring surcease to the patient and to the physician who attends him but the results are relatively ephemeral. Electroshock is also widely used to maintain feasible interpersonal relationships in an otherwise disturbed ward. Now, however, violent patients can be managed in an open ward by methods which are less drastic than electroshock and with more enduring results than those of the barbiturates. The new pharmacological agents appear to be of a different order so that a term is now applied to drug action with new meaning, that is, tranquillization to connote sedation without hypnosis. Fabing has suggested the term ataraxia, denoting peace of mind, to describe the action of the new psychopharmacological agents.[2]

What are these drugs? What have they accomplished? What are their mechanisms of action? What is in store for the future?

*Clinical Evaluation.* The two new drugs have had many names attached to them but the accepted generic nomenclature refers to them as chlorpromazine and reserpine. Though the effects of these drugs are still under active investigation we already have a considerable body of knowledge on the clinical actions of these drugs and they will be referred to briefly.

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From Thudichum Psychiatric Research Laboratory, Galesburg State Research Hospital, Galesburg, Illinois.

Reports reveal that patients with schizophrenic reactions in catatonic or paranoid excitement, manic depressives in the hypomanic or manic stage, patients with agitated senile reactions, acute obsessive states, tension states and acute anxiety are helped by chlorpromazine.[3,4,5,6] In fact, a component of overactivity in the patient suggests a favorable usage of these drugs and for that reason, the more disturbed the patient, the more dramatic are the results obtained with this tranquilizing drug. In contrast, patients with burnt out schizophrenic processes who are regressed and without active hallucinations and delusions are not as favorable subjects for this form of therapy.[7] Nor are patients with depressive reactions without anxiety and tension, patients who suffer from chronic anxiety neurosis with extensive somatization, likely to be helped.[8]

In general the same therapeutic delimitation has been reported for reserpine.[9] Patients who had been assaultive, resistive, raving and denudative were so improved that they were able to return home.[10] Disturbed, psychotic patients could be removed from maintenance electroshock treatment. Even some of those who had responded poorly to electroshock could be sent home after receiving reserpine.[11]

The distinction between the results obtained on excited patients and those with apathy is again seen in the effects of reserpine on geriatric disorders.[12] The proportion of elderly psychotic patients who were irritable, quarrelsome and apprehensive, revealing improvement on reserpine, was greater than that of the patients who showed chiefly depression, negativism, apathy and withdrawal. In fact, the chronic administration of reserpine may produce such untoward response as withdrawal, lethargy and unhappiness but not anxiety.[13] Chlorpromazine, too, may evoke depression with obsessive features.[7]

The advantages of these two drugs are not limited to the hospital and a greater number of discharged patients, but are also extended to the physicians' office because more psychotics can now be treated on an ambulatory basis. Neuroses have also been satisfactorily managed. Patients with stubborn anxiety and signs of tension are rendered relaxed and comfortable and are able to go about their daily duties with less effort. There are other than therapeutic advantages involved. Whether in private practice or in the hospital these treatments are less expensive than the standard ones, and the factor of economy is a large one. The highly trained personnel required by the standard treatments will form a smaller factor for consideration in the future. Among the benefits afforded by these drugs must be included a better atmosphere on the ward, affecting both patients and personnel.

My experience, gained in association with Doc-

tors L. H. Rudy and F. Rinaldi is concerned with approximately 40 patients on whom the effects of Frenquel, a more recent advance, as well as of reserpine and chlorpromazine have been evaluated in turn on the same group of patients.[14] At this time I would simply like briefly to point out some clinical differences among these three drugs, keeping in mind the fact that our conclusions apply to the small number of patients we have studied. Both reserpine and chlorpromazine were effective in the treatment of patients with paranoid reactions. We, however, regarded chlorpromazine as better for this clinical category and especially so because reserpine activated the symptomatology of two of our patients. In the tranquilization of patients with schizoaffective reactions, chlorpromazine also appeared to be the drug of choice. On the other hand, the patients with hebephrenic reactions, as well as those with mixed hebephrenic-catatonic reactions benefited more from reserpine. Though the members of the last two groups exhibited better ward adjustment and management with chlorpromazine, they did so at the price of aggravation of the symptoms of withdrawal, apathy, passivity and seclusiveness. Similarly, reserpine produced an improvement in one patient with involutional depression, yet on chlorpromazine his condition became worse. Taking into consideration all the clinical categories we found that reserpine produced a greater number of improvements in our moderaelty disturbed and chronically ill patients.

Frenquel, too, was of value and induced beneficial effects on our patients with schizophrenia. Some of these belonging to the paranoid group, revealed a moderation in the intensity of their hallucinatory and delusional experiences with resulting improvements of behavior. Ward adjustment became better as hostility and overactivity diminished.

More appropriate behavior was also observed in the hebephrenic and hebephreno-catatonic patients as their thought processes and speech became more comprehensible and logical, while catatonic features were rendered less prominent in intensity and duration.

In a comparison of the effects of Frenquel with those of reserpine and chlorpromazine a difference was noted, in so far that one or the other of the latter two induced in some patients of each clinical category a degree om improvement greater than that attained by any patient under Frenquel. Thus the modifications of behavior induced by Frenquel were neither so extensive nor so marked as were those observed following the use of reserpine and chlorpromazine. Yet when weighing Frenquel on the balance, its greater safety and freedom from side effects are arguments in its favor. Certainly this tranquilizing drug was valuable in the treatment of our moderately disturbed and chronically ill patients.

*Physiological Analysis.* Experience has taught that drugs have multiple sites of action, each with different thresholds of susceptibility. This aphorism applies not only to the various organs of the body but also to the component parts of the brain. Though the final effect of a drug must be defined in terms of its integrated action on the entire body, yet for the sake of convenience the influence of chlorpromazine and reserpine on different brain structures will be considered separately.

The consensus in regard to both drugs is that they depress the hypothalamus, the portion of the brain which, as demonstrated by Cannon and his students, notably Bard,[15] contains the patterns for mobilizing the organism for the fight and flight reactions. In this area are found centers for the control of basal metabolism and temperature, the sleep-wakefulness cycle and blood pressure. In addition the hormonal balance is changed as the support afforded to the anterior pituitary gland is reduced by hypothalamic depression. The amount of gonadotrophic hormones released by the anterior pituitary is decreased[16] and for that reason menstrual disturbances are observed.[17] The anterior pituitary is rendered less susceptible to stimulation and that has an effect similar to that evoked by lowered production of overaian hormones, a phenomenon which brings on lactation.[17] Chlorpromazine[18] influences hypothalamic functions in such a manner that basal metabolism is decreased and body temperature lowered. Blood pressure falls and sleep is facilitated as barbiturates and other hypnotic and narcotic drugs are potentiated. Most important for the treatment of disturbed patients is the fact that the posterior hypothalamus, containing sympathetic centers is so affected by chlorpromazine that patterns for emotional expression tend to be inhibited. The central action which serves to diminish blood pressure is greatly enhanced by the chlorpromazine blockade of the sympathetic ganglia. Heart rate is increased, in part due to an atropine-like action but also in response to a fall of blood pressure. This drug-induced fall of blood pressure, in addition to the depression of metabolism and of temperature, explains why chlorpromazine is an essential part of the hibernation cocktail.[19] With a fall in basal metabolism temperature and blood pressure, the blood supply dwindles and operations are rendered relatively bloodless. Such a change, favorable for surgical procedures, should, however, be carefully controlled so that systolic pressure does not fall below 55 to 65 mm Hg. For brain operations the patient should be kept in the Trendelenburg position as elevation of the head to reduce bleeding further can produce permanent cerebral damage.

Reserpine, like chlorpromazine, depresses hypothalamic mechanisms but in contradistinction to chlorpromazine does not exert direct effects on peripheral nerve structures.[20] The inhibition of the sympathetic representation in the hypothalamus explains the fall in heart rate, the drop in blood pressure, the constriction of the pupils and the increased intestinal activity. These parasympathomimetic effects, however, are not caused by peripheral stimulation of parasympathetic nerves nor by peripheral inhibition of sympathetic nerves.

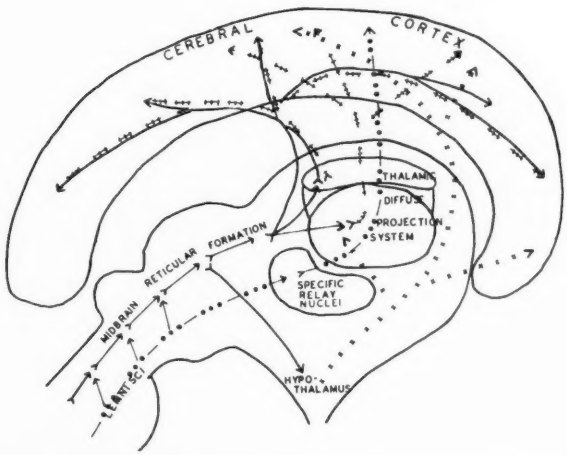


*Figure 1.* Mesodiencephalic Activating System.

Stimuli from the periphery of the body evoke impulses which travel via the lemnisci through the specific relay nuclei of the thalamus and thence to specific sensory areas of the cerebral cortex. The lemnisci send collaterals to the mid-brain reticular formation and by these paths impulses advance through that formation to the thalamic diffuse projection system, which in turn arouses the cerebral cortex in a diffuse manner. Collaterals from the mid-brain reticular formation also pass to the hypothalamus and carry impulses from that area by way of the diffuse system to the cerebral cortex.

*Neuroelectrical Analysis.* Dr. Franco Rinaldi and I, working on rabbits, reported another central site for the action of these drugs, namely the mesodiencephalic alerting system.[21,22] Historically this system is built up of two portions, the reticular formation of Moruzzi and Magoun[23] and the thalamic diffuse cortical projections of Jasper[24] (see Figure 1). The two parts may, however, be regarded as acting together and for brevity will be termed simply the activating system. Probably collaterals from the lemnisci carry afferent impulses to the reticular formation. The hypothalamus is involved in the function of the activating system as the excitatory process is conducted from the reticular formation to the subthalamus and hypothalamus in turn and thence back to the cortex either directly[25] or via the thalamus.[26] When this system undergoes stimulation, the alerting, arousal or awakening EEG pattern is produced. As, however, excitation diminishes or ceases, the sleep or drowsy pattern is observed. The drowsy pattern is characterized by slow waves of high amplitude interrupted by 14 per second spindles and the alert pattern by low amplitude rapid waves in the cortex between 20 and 30 per second as well as a continuous repetition of 4 to 7 per second waves in the thalamus (Figure 2). Not only is the arousal reaction evoked by nervous stimuli but it is facilitated by central nervous system stimulants as for example amphetamine or Meratran (Figure 3). In contrast, drugs inducing sleep like the barbiturates are associated with the drowsy pattern. An early effect of barbiturate depression is the development of high voltage fast frequencies but the latter gives way to slow delta waves as presented in Figure 4.[27] Though there are exceptions to the rule,[28,29]

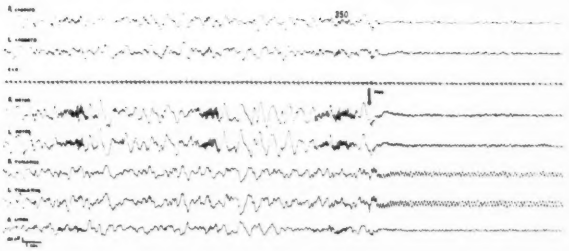

*Figure 2.* Peripheral Stimulation arouses Activating System.

An impulse from the periphery evoked by pain activates the alerting mechanism and changes the drowsy pattern to one of alertness. The left part of the figure reveals the resting pattern of high voltage slow waves and 14 per second spindles. The right part of the record shows cortical fast low voltage activity and 4 to 7 cycles per second rhythm of thalamic origin.

Records are derived bilaterally from the limbic cortex, the motor cortex, the caudate nucleus and the thalamus. In addition an ECG record is presented.

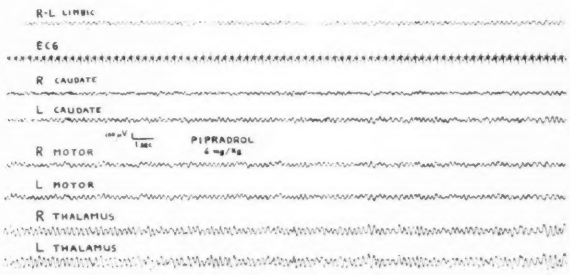


*Figure 3.* Alert Pattern Evoked by Meratran (Pipadrol).

The EEG pattern produced by 6 mg/kg of Meratran (pipadrol) is essentially one of enduring alertness. A thalamic rhythm of 5 cycles per second is seen while low voltage fast activity is dominant in the motor cortex and the caudate nuclei.

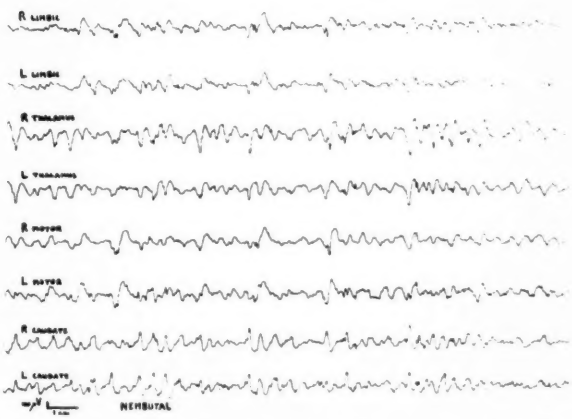


*Figure 4.* Effect of Moderately Deep Barbiturate Depression on Brain Waves.

Slow, 1 to 3 cycles per second, waves become diffusely dominant over the entire record as the activating system is depressed by pentobarbital (Nembutal).

in general it may be said that behavioral arousal is associated with stimulation of this activating system and behavioral sleep with its depression. The effect of a pain stimulus to evoke the arousal reaction is seen (above in Figure 2) but chlorpromazine in small doses[29] blocks such a response. For example, the pain stimulus no longer is capable of producing the alert state. This drug therefore diminishes the inflow of stimuli to the cortex and we

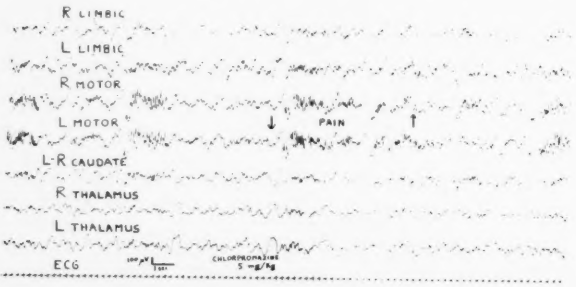


*Figure 5.* Alerting Effect of Stimulus Prevented by 5 mg/kg of Chlorpromazine.

Note the absence of the alerting reaction to pain due to comparatively low doses of Chlorpromazine. Comparison with the control record (Figure 2) reveals the similarity of the Chlorpromazine-produced pattern to the normal sleeping picture.

observe an inhibitory action (Figure 5). Thus in addition to the depressant effect of chlorpromazine on the hypothalamus we find a second site for depression in the activating system. According to Gellhorn the latter is involved in a diminution of the affect.[26]
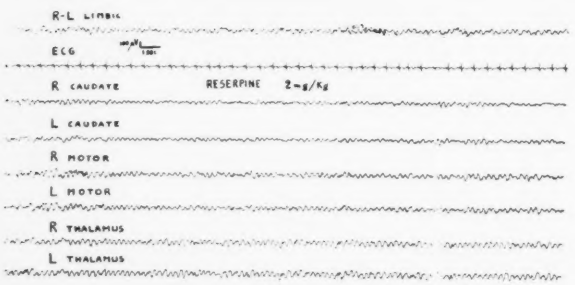
*Figure 6.* Enduring Alert Pattern Induced by Reserpine.

The resemblance of this picture to the normal alert pattern is due to the absence of high voltage slow activity and sleep spindles. Instead we observe low voltage fast waves in the cortex and a regular 4 cycles per second thalamic rhythm. Note bradycardia induced by Reserpine.

Reserpine, in comparatively small amounts, stimulates this activating system[29,30] (Figure 6). With doses of 0.5 mg/kg or less little change is seen, from 0.5 to 1.0 mg/kg alerting is facilitated while from 0.5 mg/kg upward a persistent alerting response is elicited. Even though the injection of reserpine was made into the carotid artery, arousal followed only after a latent period of from 20 to 30 minutes. This alerting response may be involved in the tranquilizing effect of reserpine. The same dose which depresses the hypothalamus may also stimulate the activating system and thus the sleep which would be facilitated by hypothalamic depression is counteracted by the arousal reaction. Chlorpromazine, when given in large doses also

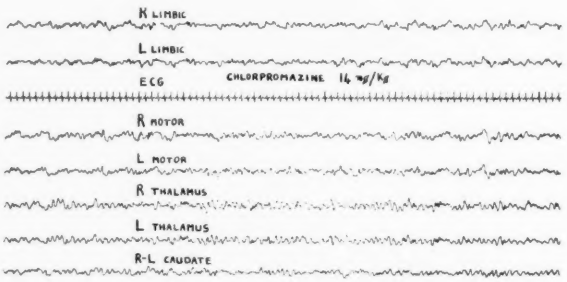


*Figure 7.* Enduring Alert Pattern Induced by Large Doses of Chlorpromazine.

A continuous arousal pattern with low voltage rapid waves in the cortex and 5 cycles per second in the thalamus is observed.

evokes the alerting response[29] (Figure 7). Thus in quantities greater than those required to depress the activating system Chlorpromazine exhibits a reversal and the activating system is stimulated. Large doses of chlorpromazine act like reserpine to evoke arousal.

A side reaction of the arousal state is the production of Parkinsonism.[29,30] As discussed by Magoun[31] the activating system possesses centrifugal effects as well as centripetal ones. The reticular formation and the reticulo-spinal tracts carry the main motor outflow of the extrapyramidal system. Experiments of Ward, McCulloch and Magoun[32] and of Folkerts and Spiegel[33] show that the overactivity of this system is responsible for the characteristic tremor of Parkinsonism. Stimulation of the activating system by these drugs may therefore produce a Parkinsonian picture just as well as by the liberation of this system from cephalad control due to lesions in the basal ganglia or the substantia nigra.[32,33]

Are the two central sites of action on the hypothalamus and the activating system the only cerebral areas influenced by reserpine and chlorpromazine? Such a statement would be rash in the present state of the rapid development of this subject. For reserpine, Schneider et al., find a facilitation of synaptic transmission in the cord.[34] They suggest that if a similar facilitation occurs in the cortex we may have an additional explanation for the hypothalamic depression induced by reserpine as the cortical inhibition of the hypothalamus is strengthened. For chlorpromazine, too, may augment the cortical inhibition exerted upon the hypothalamus.[7]

I feel sure that we have not completely elucidated actions of these drugs on the brain. The importance of the activating system may not be limited only to the prevention of such hypnotic effects as can be evoked by the barbiturates nor by

the production of the side reactions of Parkinsonism. It is probable that depression of the hypothalamic sympathetic mechanisms mitigates the severity of the psychotic symptomatology. The present observations, however, do not extend the action of these drugs to the cortex which presumably is involved in hallucinatory and delusional experiences. Still another site is suggested by Frenquel which does not depress the hypothalamus and yet appears to be effective therapeutically. In a group of patients with acute psychotic episodes, Fabing has obtained striking results.[2] In our series of moderately disturbed delusional and hallucinatory patients we have also seen improvements.

How then are we to explain the salutary action of Frenquel on the psychotic patient? The only hints that we have are suggested by the observations of Fabing that Frenquil benefits model psychosis induced either by LSD (d-lysergic diethylamide) or Mescaline.[35] In animal experiments we observed that LSD or Mescaline induced the arousal reaction. This is not characteristic of hallucinogenic drugs only, because many central nervous system stimulants like amphetamine and Meratran (see Figure 3) can also evoke the arousal responses.[29] When Frenquel is injected subsequent to either amphetamine or Meratran it does not reverse the arousal response but, when Frenquel is administered after LSD or Mescaline the alerting reaction is eliminated from the EEG and the resting pattern is restored[36] (Figures 8 and 9).

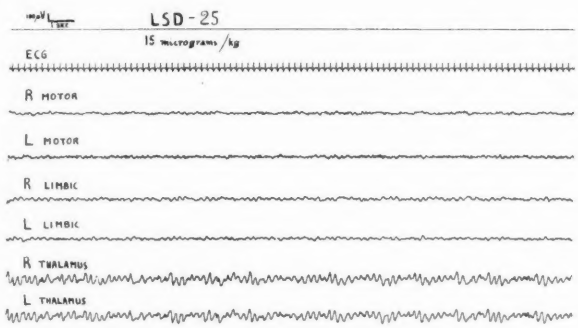


*Figure 8.* LSD Evokes Alert EEG Pattern.

The abnormal pattern induced by LSD presents fast low voltage activity and 4-6 cycles per second thalamic waves.

The lead afforded by Frenquel is suggestive because the low amplitude rapid frequency waves produced by LSD and Mescaline are also found in untreated human subjects. Though such waves have been reported in but few so-called normal individuals, they occur in about one-third of the patients with schizophrenia, manic-depressive reactions, psychoneurosis and more than half of the patients with involutional psychosis exhibit such waves.[37,38,39,40] The mechanism for bringing about this low amplitude, fast activity is unknown. It may be due in the first place to a disorder of the cerebral cortex. Another suggestion is that it represents the effects of an overactive alerting system upon the cortex. It is hardly likely that a peripheral stimulus is the cause of such overactivity. We must therefore seek for a central site in some structure of the brain, perhaps in the cerebral cortex. Under such conditions we might have a positive feedback. Not only does the cortex stimulate the activating system but the activating system in turn stimulates the cortex and so we have a vicious cycle. One way to test such susceptibility is to administer Frenquel to patients with low amplitude, fast activity and see whether or not it can be eliminated. If Frenquel is successful in reducing fast activity it may not be impossible that there is an association between the electrical hyperactivity of the brain and the psychotic process and that both are inhibited by the action of Frenquel.

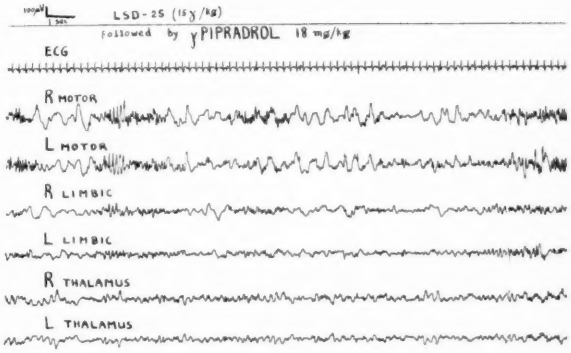


*Figure 9.* Frenquel (Gamma-Pipadrol) Eliminates Abnormal EEG Pattern Induced by LSD.

The slow waves and 14 cycles per second spindles, abolished by LSD (see Figure 8) reappear on the normal drowsy electrical pattern is restored by Frenquel (gamma-pipradrol) (azacyclonol).

*Neurochemical Analysis.* I have briefly reviewed some of the behavioral results obtained by the use of Frenquel, reserpine and chlorpromazine. The alterations produced by these drugs, the clinical improvements, are explained in part by the observations made on animals as well as human subjects, including such pharmacological effects as depression of hypothalamic mechanisms. The observations made with the aid of the EEG were also helpful for they disclose additional aspects of drug action on the activating system. But what are the biochemical changes which are the source of the pharmacological actions inducing alterations in behavior? Experiments of Grenell and associates[42] revealed that when chlorpromazine was injected into rats and brain tissue was analyzed, changes in oxidation of the excised cerebral tissues were not observed. These results are in agreement with others on cerebral metabolic rate obtained in the human subjects who had received reserpine[43] or chlorpromazine.[44] However, a significant alteration was observed in excised cerebral tissues, an accumulation of energy-rich phosphates in the form of adenosine triphosphate (ATP).[39] This accumulation could be due either to the accelerated production of ATP or its slower utilization. According to the authors the latter is the correct interpretation. It may be of some importance that the midbrain region of the

rat containing the thalamus and hypothalamus showed a greater increase of ATP than any other cerebral part as a result of chlorpromazine.

The next step in our inquiry is to determine the cause of the changes in brain metabolism and the answer to this question may involve the neurohormones of the brain. In that regard the experiments of Hoffer, Osmond and Smythies[46] on a breakdown product of adrenaline should be considered. These workers observed that a substance contained in a pink or deteriorated adrenaline solution evoked hallucinations. They believe that the hallucinogenic substance includes the indole nucleus as part of its chemical structure, and also pointed out that some

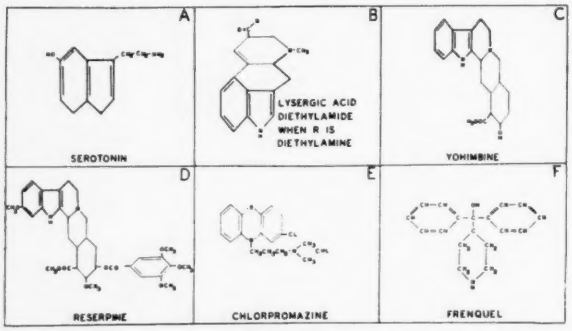


*Figure 10.*

A. Formula for Serotonin.

Note indole nucleus and 2-carbon side chain terminating in a nitrogen containing group.

B. Formula for LSD (d-lysergic acid diethylamide).

Observe indole group and part of side chain similar to that of serotonin, represented by thickened lines.

C. Formula for Yohimbine.

The similarity of yohimbine to serotonin is apparent.

D. Formula for Reserpine.

Note striking similarity in the chemical structure of this tranquilizing drug to that of yohimbine.

E. Formula for Chlorpromazine.

F. Formula for Frenquel.

The chemical structures of the two tranquilizing drugs, Chlorpromazine and Frenquel, differ from those of the four preceeding substances. This figure is a modification of that presented by Woolley and Shaw (50).

hallucinogens like LSD, harmine, medmain, yohimbine contain this indole nucleus (Figure 10). In fact Rinkel et al., have suggested that LSD may influence the enzyme system concerned with the metabolism of adrenaline.[47] Marrazzi and Hart[48] as well as Liddell and Weil-Malherbe[49] emphasize disturbance of an adrenergic neurohumoral mechanism. Woolley and Shaw[50] were also struck with the similarities in the chemical structure of the hallucinogens but their viewpoint was somewhat different as they stressed the resemblance to the neurohormone serotonin (5-hydroxytryptamine) found in smooth muscle as well as in the brain. They suggest that these pathogenic substances act as antimetabolites, combine with the same receptors as serotonin but prevent the normal response elicited by serotonin. In addition, evidence in a paper by Shore, Silver and Brodie[51] reveals that serotonin in large doses is sedative and potentiates the action of Evipal, an ultrashort-acting barbiturate, in mice. This central action of serotonin is blocked by pretreatment with LSD (52) thus implicating serotonin in brain function and lending support to the suggestion of Woolley and Shaw that abnormal mentation is due to the blocking of serotonin receptors. Reserpine, like serotonin, potentiates Evipal (51) an action also prevented by LSD. Reserpine, which resembles serotonin in chemical structure (see Figure 10), cause the liberation of serotonin. The evidence for this conclusion was obtained partly on dogs, for reserpine increased their urinary excretion of a metabolic product of serotonin, namely 5-hydroxyindoleacetic acid (5 HIAA).[52]

Further experimentation showed that reserpine has a biphasic action on serotonin, not only an early and temporary increase, but also a late and enduring diminution.[53] Perhaps the continued injections of reserpine would prevent serotonin from attaining normal values and in that case the benefit derived from reserpine lies in a decrease of serotonin. If these results yield a clue to the action of reserpine on the brain, and this is yet to be proved, then I would like to offer a tentative explanation for the therapeutic effects of reserpine, namely, that the abnormal activity of disturbed psychotic patients is associated with an excess of serotonin and that under continued dosage of reserpine the concentration of serotonin in the brain is reduced. In accordance with this speculation, the lag in the clinical effects produced by reserpine represents the time necessary for the elimination of serotonin from the body and perhaps lowering its concentration in the brain. Furthermore, the continued pharmacological action of reserpine after that drug is withdrawn may indicate the period necessary for the restoration of the serotonin depots.

It is of interest that both chlorpromazine and Frenquel potentiate Evipal though Frenquel is weaker than chlorpromazine in this regard. The administration of chlorpromazine does not, however, increase the excretion of 5 HIAA. It would appear that these drugs act like serotonin. They are serotoninmimetic and go to the same receptors as serotonin thereby reducing the effectiveness of that neurohormone. This viewpoint is the opposite of Woolley and Shaw[50] and suggests that abnormal mention is associated with an excess of serotonin while a reduction in the concentration of serotonin is therapeutically beneficial.

Recent experiments, performed in our laboratory by Dr. E. Costa,[54] have yielded additional evidence for such a conception. Using the rat uterus as a test object he observed that the uterine contraction produced by serotonin is blocked by each of the three tranquilizing drugs. The block evoked by Frenquel is of shortest duration, that induced by chlorpromazine lasts for a longer time, while the effect of reserpine is the most enduring of the three. Perhaps that is the reason why reserpine

is the most effective of the three agents in causing the release of serotonin and the excretion of 5 HIAA. Furthermore, Dr. Costa, has found that LSD and mescaline potentiate the uterine contraction caused by minimal doses of serotonin. This observation does not contradict that of Gaddum and Hameed[55] who found that LSD inhibits the maximal contraction induced by serotonin. Thus, at least for the rat uterus, the three tranquilizing drugs reduce the effect of serotonin, while in contrast LSD and mescaline augment its action. Though these experiments are suggestive, their significance in regard to the function of the brain will require further work.

*The Future.* What has the future in store? Before making an attempt to define the paths of further progress it is well to examine our present position. Most physicians who have tested these drugs are convinced that they are a great step forward. The beneficial effects are not a "flash in the pan," but have been widely corroborated. We can therefore look with satisfaction at the progress we have made. Do we cure our patients? Until we have unearthed the roots of schizophrenia the answer to this question remains a semantic one. But now the psychiatrist has at his command drugs which are of aid in wiping out the symptoms of psychotic patients just as the internists can use insulin for the elimination of the symptoms of diabetes.

Added to our armamentarium are drugs which aid in the control of disturbed psychotic patients. These drugs are effective not only for disturbed patients with psychomotor overactivity but also for emotionally tense ones with acute anxiety. The value of these drugs is being tested for various clinical categories and in general one might predict that in many conditions for which bromides were formerly used and now barbiturates are prescribed, the new drugs will receive preference.[56,57]

Therapeutic evaluations reveal that they are not the complete answer for our problem. All these drugs are tranquilizers. Though they are used successfully against depression associated with anxiety and tension, we will still await the pharmacological agent that is as effective as electroshock for melancholia. The plans for the immediate future also involve a consideration of some of the inadequacies of these drugs. Both chlorpromazine and reserpine exhibit undesirable side reactions and efforts are now being bent toward their alleviation.

More important is the observation that not all patients were helped equally by any one of these three drugs and those of some clinical categories are benefited more than others by each of them. The discovery of additional pharmacological agents therefore becomes imperative. The suggestion from reserpine and chlorpromazine that drugs must depress the hypothalamus to be effective should be considered as it is apparent that such a depression will mitigate the severity of emotional expression both in somatic and mental terms. A second site of action is found in the activating system. Frenquel suggests the possibility of still other loci. One way to attain this goal of discovery of new therapeutic agents is indicated by past experience. Variation in chemical structures of the drugs now used may induce new and unexpected actions and such variants should and will be evaluated clinically. But drugs of entirely different chemical constitution must be produced, perhaps with specific affinities for the receptors of neurohormones in the brain. Recent evidence from Brodie's laboratory, as well as our own, indicates that the tranquilizing drugs alter behavior by their influence on serotonin.

We are living in a moment of excitement, rich in potentialities that can be realized by increased interaction between psychiatrists and pharmacologists. We cannot help but feel that the advances made by chlorpromazine and reserpine, important as they are, represent only the initiation of a new era in psychiatry. The advent of Frenquel may be regarded as another harbinger of such an era. The science of psychopharmacology has come to stay!

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# Effects of Partial Perceptual Isolation in Mentally Disturbed Individuals

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The purpose of this paper is to present the results of a study of partial perceptual isolation which has yielded some information about the problem of depersonalization and body-scheme.

The impetus for this study came from three different lines of inquiry.

A. The problem of the patient disorganizing in psychotherapy which under certain conditions yields beneficial therapeutic results. Recent experiments with hypnosis,[1] anaclitic therapy,[2] prolonged sleep treatment[3,4] and "regressive electroshock therapy"[5] all have indicated that in an appropriate setting if the opportunity is provided for the organism to regress (in action and in phantasy) to those stages of development where it has been fixated and its growth vitiated, a reverse impetus for progression and re-organization may ensue.

B. Studies of Perceptual Isolation in Hebb's laboratory. Thompson and Heron[6] reporting the effects of restriction of the environment on exploratory activities of dogs, and later experiments of Bexton, Heron and Scott[7] on the influence of decrease variability in sensory environment of "normal" human subjects, demonstrated the disorganizing effects and reduction of partial isolation. The importance of isolation has been emphasized in the reports of political prisoners who have become disorganized and "brain-washed," and in the subsequent reorganization stages have shown an alteration in their former ideational defence patterns.

C. A wide variety of reports have dealt with the problems of body-image, body boundaries, body-ego, social field, depersonalization, sytle of being or "being-in-world" (The dasein of Existential Philosophy) or what Scott[8] has reconceptualized as the Body-Scheme. All these problems deal with the relationship of the individual to his world. It was felt that perceptual isolation may allow us to study this relationship under altered conditions.

### *Method*

Five patients suffering from anxiety states, two obsessive compulsives, five depressions and two hebephrenics were put on partial perceptual isolation for a period of time ranging from two to six days. Except for two depressed cases whose ages were 50 and 60 respectively, the ages of 11 of the patients were below 40.

The isolation setting consisted of an ordinary single hospital room containing all facilities, and situated farthest from the center of the ward. The room was darkened by means of heavy curtains on the windows. The patient remained in the room throughout the isolation, lying or sitting in bed, wearing translucent eye-goggles, and with hands and arms encased to a few inches below the shoulders, in cardboard cylinders. Patients were put on demand feeding and demand evacuation, and if possible they were fed with the apparatus on. Face and teeth were washed once a day. Except for the dark setting and some changes in nursing care the apparatus was quite similar to the one used by Bexton, Heron and Scott.[7] However, the technique used here differs in two major aspects from those of the above menitoned authors: The first is the motivation and psychological attitude of the subjects, and the second the relative decrease of verbal relationship. Before isolation the procedure was explained in detail to the patient as a method of investigation and treatment, aiming at cutting down external stimulations. They were told that they could terminate the procedure any time they wished. The patients accepted the isolation mostly with optimism, and as a means for recovery from their psychological handicaps. The decrease in relationship was partially realized by cutting down the verbal exchange with the patient. Patients were checked once every hour, but they were interviewed or tested only once or twice a day for a period ranging from 15 to 30 minutes, (the glasses were removed during the testing period). This interview was conducted more or less in a psychotherapeutic setting. The changes in psychodynamics were investigated through the analysis of patients' dreams, fantasies, free associations, figure drawings and Rorschachs. All the patients were tested before and after the isolation with a partial Wechsler Bellevue scale and figure drawings, (F.D.) Rorschachs were redone on those patients who had had the test prior to the isolation. During isolation figure drawings were repeated every other day. Three patients were investigated in regard to their vestibular apparatus before and after isolation. The reason for this was that emphasis some of the authors like Schilder had placed on the important role of vestibular apparatus on maintenance of body-image. Most of the patients were on supportive form of psychotherapy.

### *Results*

We shall limit ourselves to a few brief case reports in each diagnostic category, with particular emphasis on the changes and emerging processes during isolation. The reasons for our refraining from a detailed discussion of the patients' pre-isolation psychodynamics will be discussed in a later portion of the paper.

In all, eight cases out of a total of 15 showed a depersonalization state with different degrees in

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intensity of visual, auditory and gustatory hallucinoses. A beneficial therapeutic effect was observed in the five depressed cases, in two this effect was permanent. The two obsessional neuroses manifested acute psychotic episodes. They were treated later with electric shock, which resulted in improvement in both paranoid and obsessional features. The remaining eight cases showed a moderate increase in motivation, socialization and self-assertiveness.

*Case 1.* A 19-year old male presenting a hebephrenic reaction was put on isolation with the purpose of promoting a regressively satisfying environment in which most of his needs would be satisfied, and his anxiety about his relationship with the world reduced. He remained in isolation for four days. During the first two days he appeared restless and manifested increasing withdrawal and blocking. On the second day he experienced an hallucinosis consisting of yellowish spots. On the third day the hallucinosis increased in variety and color, for short periods of time: e.g. "I see flickering of light, sort of yellowish. Sometimes I see different designs." He also reported, "I can't identify what I am drinking any more. . . . I imagine sometimes that I am not in this room, that my bed is in the hall. It feels funny, I know I am not in the hall." On the fourth day he experienced an increase in both hallucinosis and feeling of estrangement: "I see different objects now, broken down shacks, pen, etc. . . . (?) sort of imagination I suppose. . . . I can't feel my arms anymore (?). My hands and legs, I just can't feel them. (What do you think has happened?) I don't know, I just don't feel them. (Patient moves his arms.) Still don't feel them. . . . Ah! It is coming back now (Where?) My left arm." Although he was quite resletss he never felt aggressive and was pleasant. The study of his psychodynamics during isolation through his figure drawing and the analysis of one dream ("My father died."), revealed repression of aggressive tendencies which was particularly evident on the fourth day (absence of hands and feet in figure drawing) associated with some increase in anxiety indices. However, F.D. revealed also some degree of re-organization (better details, better proportion, etc.) increasing need for social contact, and oral demands. Post-isolation cognitive tests showed some mild improvement in concentration, and intellectual functioning. Clinically, during the Post-isolation period he showed a transitory improvement which lasted about four days. He became more communicative, was less vague and more cheerful.

Contrary to the above case, a hebephreno-catatonic girl who remained in isolation for six days showed no perceptual alteration. Behaviorally, she manifested overt hostility, became quite talkative and self-assertive. Her F.D. revealed gradual, but definite emergence of aggressive tendencies. She also xperienced several spontaneous orgasms, and verbalized memories of her "sexual adventures."

*Case 2.* A 30-year old female suffering from a depressive state, which had become manifest a year previously, after the birth of an unwanted illegitimate child. She accepted isolation and tolerated it for six days. During the first two days she felt "lonesome," and tried " to hink things over." On the third day, she reported: "My head occasionally starts to spin, and then sometimes I feel I am not here, I don't know where I am (?) I just don't know. It takes about half an hour or more to think back and get my bearings. . . . It is unpleasant, I get scared." She had similar, but more intense experiences on the fourth day. On the fifth day she reported: "Sometimes I don't feel the bed. It goes away (?) I feel that I am in the air floating. I don't like it. It lass about 10-15 minutes. I float lying down as in a cloud (?) I can't explain it, you have to go through it to know. I don't feel anything, my arms weren't there from shoulder down. . . . I feel also that my bed occasionally is rocking, swinging." On the sixth day these feelings began to decrease, the patient became restless, resentful, broke an arm band, and demanded the termination of isolation. Throughout isolation, except for the last day, she had remained calm, rather cheerful, very co-operative, and dependent.

The study of her psychodynamics during isolation with the aid of five consecutive dreams, and her F.D. revealed the emergence of aggressive tendencies in the first few days, and its subsequent suppression and introjection. She dreamed for three nights that she was "in a boat with her father fishing" (with the doctor in isolation). This was followed by "the doctor eating . . . a cow killed, blood on the snow." (She kills the doctor because she feels sexually assaulted by him. Patient is frigid like snow); and afterwards the dream of "going home in a train" (possessing father's penis) . . . a train wreck, a woman bleeding (she punishes herself for killing her father, etc.) These dreams were not interpreted. The analysis of figure drawing brought out a rapid withdrawal, depression associated with evidence of repressed aggression (sudden decrease in size, loss of hands and arms, oral amphasis).

In the Post-isolation period the patient showed considerable clinical improvement. Her mood changed, she became more communicative and self-assertive, she began to pay more attention to her appearance and manifested a desire to socialize.

Concomittantly, psychological tests showed immediate increase in feelings of well being, increasing desire for socialization. In post-isolation there was slightly improved efficiency on the intellectual sub-tests and the F.D. were better organized. The improvement continued for four days and then gradually the patient returend to her former state and was put on electric shock therapy.

We draw attention to the difference between the overt behaviour of the patient during isolation (calm, cheerful, dependant) and her overt tendencies of destructiveness. The study of vestibular sensitivity before and after isolation showed no abnormality.

*Case 3.* A 41-year old female suffering from recurrent attacks of depression, the last of which had started two months prior to her admission. It was noted that a previous attack had been precipitated when a doctor told her that her son's tooth should be extracted, and a second episode followed the death of her father-in-law.

She remained in isolation for five days. During the first day she was quite restless, and had vivid day-dreams of being or having been home. On the second day she stated: "When I woke up, I didn't know where I was . . . I felt quite dizzy." On the third day she reported: "It seems that at times I am losing parts of my body . . . my legs, as if there was nothing in bed (?) I thought I went to sleep, but I wasn't. It is hard to describe, I am in bed, then a minute later I am not there anymore . . . as if I had lost control of my body. Movement does not bring my body back. I was surprised at first, then I said, 'oh, well!" During the fourth day these experiences increased in intensity: "I felt I had no body at all, just head and arms. I know I have them . . . I wait till it comes back." The patient had no feeling of anxiety, and remained calm throughout isolation, but because of increasing depression, isolation was terminated.

The study of her dynamics during isolation through figure drawings showed increasing aggression, (gradual increase in size, the appearance of fingers and toes from the second day on, oral amphasis, etc.) A considerable disorganization in the drawings was noted on the second day just prior to the development of a depersonalization syndrome, followed by decrease in tension an agitation. On the fifthy day, the findings in the drawings (appearance of ears), and in Rorschach suggested the beginning of a projection of aggressive tendencies.

In the post-isolation period the patient showed a relatively rapid improvement. Her mood changed, she became cheerful and self-assertive, and began to socialize. This improvement continued and the patient was discharged with no further treatment. Her F.D. and Rorschach showed increasing organization, decrease in tension, and reversal of mood. There were no gross changes in other psychological tests.

In this particular case it was felt that the disorganization initiated by isolation was followed, clinically and in psychological tests, by a rapid type of rebound process of reorganization. It seemed that, at least in part, the reorganization and mood changes could have been attributed in part to the projection of aggressive impulses.

It should be noted that of three other depressed cases who accepted isolation, one showed marked improvement leading to her discharge, and another moderate temporary improvement. Behaviorally and psychodynamically all showed overt and considerable aggression, one of them actually wanted to attack the therapist. The case which recovered under isolation was a 30-year old female who manifested, in addition to overt hostility, marked sexual phantasies and day-dreams. She perceived isolation as representing a sexual intercourse with the therapist, and brought out vivid day-dreams related to pregnancy and childbirth. She showed similar psychodynamics in the figure drawing (the female figure in the drawing became pregnant at the beginning of isolation and at the end of the treatment the female was drawn holding a baby). In this case, it appeared that isolation had resulted in a release of aggressive and libidinal impulses, with considerable gratification in phantasy. These three cases manifested no changes in body-scheme or in perceptual fields.

*Case 4.* A 39-year old female who was suffering from an obsessive-phobic state with exacerbation and remission since the age of 19. At the onset, the phobia was related to having swallowed a fish bone, then a piece of glass, and for the past four years of the fear of dying. This fear had increased gradually, had remained refractory to all types of therapy and had become incapacitating.

She remained in isolation for four days. The first day she experienced an increase in her anxiety and fear ("This is like dying.") She was unsure about continuing isolation, and once came out of the room. However, she persuaded herself to stay in. We draw attention to this fact because it appeared that this acceptance, of what could be interpreted as a symbolic death, might have had some correlation with the depersonalization syndrome which developed the following day. She reported on the second day: "I see silver stuff jumping up and down . . . my spine seems to be missing. I know it is there, but I feel I have no bones. I feel myself going up and down, swaying and then I go around . . . I feel floating in the air." She also experienced marked sweating of hands, and difficulty in "controlling my thoughts." On the third day the hallucinations increased, and on the fourth day she reported in the morning "when I shut my eyes I see foolish looking faces . . . then I see flowers of all sorts . . . I hear music, too. They stop occasionally. I don't know why I should see them, I know they aren't there." The changes in body feelings continued with additional feelings of "being turned upside down, feeling up in the air, etc." In the afternoon of the fourth day, she developed frank paranoid tendencies. "I see myself dead in a box. I see them looking at me. I think he is going to kill me (who?) my boy friend . . . I have no more power to stop my thoughts." The isolation was terminated at this time, and the patient was put on electric shock therapy which resulted in almost complete recovery of paranoid as well as phobic ideation.

The behavior of the patient throughout isolation was indicative of great anxiety, but very little overt aggression. Figure drawings showed immediate denial of aggression on the first day (prior to depersonalization) and evidence of break in the defences and disorganization on the third day. Although in Rorschach, there was evidence of some paranoid tendencies, there were also some signs of reorganization such as increased productivity, and more use of human concepts. The cognitive tests showed somewhat lowered attention and concentration.

Another case of obsession neurosis, suffering from severe motor compulsions, who had not responded to any form of treatment, was put on isolation with the explicit aim of provoking a psychotic disorganization. He remained five days on isolation, began to manifest signs of depersonalization on the second day, and showed several acute psychotic episodes, lasting about three hours on the fourth and fifth days. The disorganization manifested itself, in part, as a marked sexual disinhibition. He experienced many spontaneous orgasms, and manifested overt erotic behaviour toward the nurses. His eating habits deteriorated, and his behaviour was like that of a very hungry child during the feeding periods. In the post-isolation period, he showed some reorganization and lost some of his motor compulsions. But because of the appearance of some paranoid tendencies, he was put on electric shock therapy, which resulted in considerable improvement and subsequent discharge. Analysis of his drawings (Fig. 1) during isolation, revealed emergence of both libidinal and aggressive tendencies, (appearance of genitals and breasts; increase in size, teeth, disappearance of hands and feet, etc.) A marked disorganization and regression of F.D. occurred (primitivization, simplification, fragmentation) concomitant with the deterioration of his overt behavior. In the post-isolation the figure drawings showed increasing re-organization. The status of vestibular apparatus was found within normal limits before and after isolation.

*Case 5.* A 25-year old female suffering from a long standing anxiety neurosis who had experienced an exacerbation of her symptoms associated with some depression for about one year prior to her hospitalization, was put on isolation for the purpose of releasing her repressed hostility, inhibition and depression. On the first day of isolation, she showed some anxiety about sexual phantasies, and expressed her concern about emerging destructive tendencies as follows: "I feel this feeling of hatred inside of me, I don't know how to let it come out." On the second day she lost this feeling completely, and reported: "I feel dizzy again, as if my head didn't belong to me, it rolls back and forth (?) I know it is attached to me, but it rolls around . . . I feel as if I were drunk . . . I saw small circles before my eyes." She talked extensively about her lack of "sexual adventures" brought out phantasies of "vividly seeing myself on my father's knees," and recalled that she had "not felt anything when my mother died." On the third day the feeling of corporeal changes increased in intensity, and she reported "my head feels too heavy for me. At night

my arms feel as if they were being lifted by an invisible force . . . I was amazed. I felt dizzy . . . going round and round the room, I felt in mid air . . . I didn't feel the bed . . . subconsciously I knew the bed was there." She also experienced paresthesias, such as tingling, pin pricks on her hands, as well as inability to identify some foods. An incidence in her childhood when she was terrified of a dog was recalled. On the fourth day, she occasionally lost the feeling of having a body and saw flashes of light before her eyes. Behaviorally, she remained indifferent and calm until the fourth day, when she became aggressive, quite self-assertive, and terminated the isolation. Concomitantly, with this, she verbalized feelings of resentment against her step-mother and her female boss.

The study of her dynamics during isolation showed a gradual internalization of aggressive tendencies, particularly in her figure drawings (closure of the mouth, decrease and finally the disappearance of hair, decrease in line pressure, etc.) At the same time there was a rather sudden disappearance of the feeling of hatred on the second day. Some degree of suppression of sexual pre-occupations were also noted in the drawings.

In the post-isolation period, the patient was no longer depressed, felt more self-assertive, and was discharged on follow-up psychotherapy.

Four other neurotic patients accepted isolation. Two of these, both anxiety states, could not tolerate isolation more than two days and became openly resentful and aggressive. They showed no perceptual or bodily feeling changes. Two anxiety hysterics remained in isolation for four and six days respectively. Both showed marked changes in body-scheme, such as the feeling of floating in the air, the absence of body parts, etc. The patient who remained in isolation for six days became gradually depressed, for the first three days clinically, and psychodynamically showed evidence of suppression of aggressive impulses (decrease in size of F.D., thinning of lines, disappearance of feet and hands, etc.) The reverse process occurred in the last three days. The patient became gradually more aggressive, self-assertive, lost her feelings of depression and terminated the isolation herself. In figure drawing she showed a sudden increase in expansivity, increase in activity and a better organization of the self-drawing. It was noted that ideationally she was using her increasing ability and self-assertiveness in a constructive manner (planning for the future, "thinking htings over," etc.) It seemed as if the early disorganization tendencies had initiated a rebound reorganization impulse. She had no changes in bodily-feelings on the last day of isolation. A study of vestibular function showed no abnormalities before or after isolation.

### *Discussion*

The foregoing data demonstrates that perceptual isolation provokes a disorganization of psychic structure which, according to the kind and quality of defenses, may lead to a psychotic state. This disorganization in most cases leads either to a temporary or to a relatively permanent reorganization of some aspects of a previously unsteady psychic state. This disorganization took the form of what is classically called a depersonalization syndrome, particularly effecting body-feelings, body image, and what Scott[8] has designated as body-scheme.

The primary theoretical problem is to determine the etiology of this disorganization and changes in body-scheme. What is the role of the decrease in sensory variability, what is the role of emergent dynamic processes, and how are they correlated? We do not think that the present data, and the information available in this area, can furnish a definitive comprehensive formulation. However, the facts permit some theoretical considerations from three relatively separate points of view: physiological, interpersonal (relationship), and intrapersonal. The separation of these three hypothese is arbitrary, and made only for the sake of the analytic clarification. No final validity is claimed for any of the following hypotheses.

(1) *Physiological hypotheses:* What isolation produces is a reduction in the variability and kind of sensory in-put. Bexton, Heron, and Scott have attempted to explain changes in cognitive functions in isolation as related to the non-specific function of stimuli, which altered the maintenance of arousal. There were few cognitive alterations in our cases, and in several of them there were some actual improvements, although we did not use all of the same tests as the above authors. However, it may be maintained that it is the quantitative aspects of the stimulus-reduction which is responsible for disorganization. According to the intensity of this reduction, sleep or disorganization may occur. In fact, in some of the patients, the quantity and the pattern of sleep was intensified and disturbed. If variability in sensory in-put is decreased to a marked degree, one may postulate that it inhibits the integrating activity of the ascending reticular system. This inhibition in turn may release some self-regulating, auto-repetitive neuronal sets[9] of parieto-temporal zones with the resulting activities which are not experienced as belonging to the self. The feeling of the absence of body parts would then be interpreted as a disengagement from the central regulating system whose function is arousal or attentive apprehension[9] of the world, and needs for its activity a constant variation in sensory in-put. Jasper's studies on diffuse projection system[10] and Penfield's centrecephalic concept[11] have thrown some light on these sub-cortico-cortical connections. Experiences similar to the depersonalization syndrome have been described[13,14] in temporal lobe lesions or stimulations, and the relationship of parietal lobe to asomatognosias is well known.

This hypothesis as such fails to explains the choice of organs from which the feelings are withdrawn, and the process of reorganization which some patients showed during or after isolation. In addition it remains to be proven that the central regulating systems require for their activities constants variations of stimuli, in particular the visual and tactile areas.

(2) *Relationship hypothesis:* It is evident that in the method of isolation described here, three major areas of relationship to the world, namely visual, tactile and verbal, are being curbed more or less in their activities. If we accept the assumption maintained by Head,[13] Schilder,[14] Lhermitte,[15] Cameron,[16] Scott[8] and others that body-scheme is a dynamic ever changing process, perpetually being

altered and reconstructed, it is consistent to state that its integrity depends on a continuous close perceptual and expressional relationship with external objects. As Sullivan[17] and Angyal[18] have stressed, the boundaries of the individual and the world are closely intermingled, and it is extremely difficult to determine a line of demarcation. Total isolation is death. Cameron's concept of "incomplete organism"[19] is such a psycho-biological formulation, which has reached its apotheosis in philosophy of existence where "Dasien"[21] or being-in-world is the unit of experience and inference.

We think that these and other similar concepts can be conceived and linked together in the unifying and unitary concept of "Relationship." We reserve the elaboration of this concept for other occasions, suffice it to say that relationship in this sense may be considered not as a physical linkage, but rather as a concept connoting the way elements or being interconnect, or, as Whitehad has stated,[21] form aspects from the standpoint of one another, constructing orderly or disorderly complexes or organisms.

Isolation disrupts this relationship, prevents interchange, and disorganizes the scheme of the body and its object relations. However, the disorganization is not random. The prevention of total relationship provokes the emergence of, and a return to less organized levels of relationships, in themselves relatively complete. It should be noted that the isolation setting with the dark room, demand-feeding, and demand evacuation, and ready gratification of oral needs, may be taken as resembling in some respect the situation of infancy. By partially incapacitating the individual's three main areas of relationship it may be conceived that he is artificially being pushed into the role of an infant whose corresponding three areas are nautrally definient, but without provoking frustration. It can be inferred that this relative anaclitic[2] setting psychologically and somatically pushed the individual into his genetically primitive position wherein the organism is still in parts, and in a state of "natural" disembodiment. In psychoanalytic terms isolation stimulates regressive tendencies, and in the Sullivanian formulation it enhances a parataxic mode of experience. The changes in body-scheme may therefore be taken as comparable to the regressively evoked states of infancy where the organism is in "bits and pieces," "Sometimes mostly being good and sometimes mostly being bad".[22] The second case of obsessional neuroses described above is a good example of this primitivization or regression of behaviour. This patient behaved quite like an infant in his eating and defecating habits.

(3) *Intra-personal hypothesis:*

This hypothesis concerns itself with the psychodynamic changes within the individual emerging during isolation. We have purposefully refrained from discussing the pre-isolation psychodynamics of each patient because (a) from the range of clinical pictures, it was unlikely that there was any common dynamic constellation upon which any single conclusion could have been made, or even expected, and (b) a review of the literature on depersonalization indicates[23,24,25] that there are dynamics referable to almost all stages of development and to almost all layers of psychic structure in individuals suffering from this syndrome. It seemed, therefore, that regardless of the importance of the underlying dynamics, the emerging processes during isolation would be of greater significance. These emerging processes were found to be related to the quantity and direction of aggressive drives. No case which expressed aggression overtly showed changes in body-scheme. It appeared that when aggressive tendencies were repressed and turned against the self the feelings referable to the absence of body-scheme occurred. There was no constant finding in regard to libidinal tendencies. The problem arises as to the relationship of this introjected or turning inward of aggression to the depersonalization states, and to the etiology of the emergence of aggression. Schematically, three theoretical formulations can be given: depersonalization as a defense, as the result of a split in the ego, or as a disorganization of the self.

Depersonalization has been considered as a *defense* by many uathors,[25,26,27,28,29,30,31] whose conceptions imply that the emergence of intense needs, be it libidinal or aggressive, causes unpleasantness, anxiety and fear, which results in withdrawal of feelings or interest from the involved organs.

Depersonalization as the result of a split in the ego due to turning in of aggressive tendencies has been upheld by some authors.[32,33] Freud, in a letter to Oberndorf[31] spoke of depersonalization as a "split in ego." Cameron's conception of the increase in tension as the cause of the disorganization of the self has similar implications.[16]

It is difficult to find much incompatibility among these concepts. The split in ego or disorganization of the self may be taken as a defense against the anxiety of annihilation or of the confrontation with the drives and their aims. The fact remains that repression of aggression was concomitant with the depersonalization. Why did aggression emerge to begin with? Tentatively one may assume that isolation was a frustrating situation, and aggression was a reaction to frustration. In psychoanalytic terms, isolation provoked frustration of libinal drives, a narcissistic injury, which evoked aggression. This aggrssion subsequently was repressed and turned against the self, causing a split in the ego. Or one may say that isolation hindered the expansionistic tendencies of the organism[19] or "power motive"[17] which resulted in an increase in tension and in part disorganized the self and in part enhanced normalization processes and reorganization.

Space does not permit further elaboration of this disorganization-organization sequence. Suffice it to say that one may be able to canalize this reorganization in definite patterns if, during the disorganization, when the organism is most vulnerable in its sets, appropriate mode of actions are imposed or

suggested to the organism. Cameron's concept of "psychic driving" and "dynamic implant"[34] are useful in this regard.

*Summary*

1. The disorganizing effects of sensory isolation on animals and normal human subjects led the authors to study this problem in mental patients for the purpose of gaining some information about the therapeutic value of the disorganization-reorganization sequence of the psychic events and about the problem of depersonalization and body-scheme.

2. Two hebephrenics, five depressions, two obsessive neuroses, and five neurotic anxiety states were subjected to a partial sensory and expressive isolation for an average period of four days (eyes covered, upper extremities maintained in a cardboard cylinder, and no verbal communication except twice a day for interviewing).

3. Two sets of changes occurred: (a) Disorganization. This consisted of the appearance of a depersonalization state in eight cases; of visual, auditory, and gustatory hallucinoses, and of paresthesias. The two obsessional neuroses developed acute psychotic episodes, were treated with electric shock with subsequent improvement of both paranoid and obsessional states.

(b) Reorganization: This consisted in marked change in mood in almost all of the depressed cases, two of which showed lasting recovery and were discharged without any other therapy. In addition, constructive aggression occurred in most cases with an increasing tendency to socialization and relationship-undertaking. Psychological tests showed no significant impairment in concentration and efficiency.

4. The common emergent dynamic process during isolation which was concomitant with the changes in body-scheme was found to be related to the quantity and direction of aggressive tendencies. It appeared that repression and aggression turned against the shelf lead to the depersonalization syndrome. The theoretical aspects of the problem are discussed and physiological, relationship, and intrapersonal hypotheses are outlined.

5. It is suggested that the imposition of some action tendencies during the disorganization state may lead to reorganization according to planned patterns, and this may be useful in clarifying the problem of "brainwashing," etc. Further research along the lines described here seems warranted.

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# Prevention of Protracted Insulin Coma by Carbon Dioxide and Oxygen

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It is customary to use either the term protracted shock or irreversible coma to designate two of the most serious complications of insulin coma therapy. These designations refer to those conditions sometimes encountered in patients who do not arouse from insulin coma in spite of the administration of adequate amounts of glucose. The term, irreversible coma is generally reserved for those cases of protracted shock which terminate fatally. The term protracted shock is used to indicate a continuation of the coma for hours or days, in spite of a normal blood sugar level. Smith[1] has recently reviewed the literature on this subject. Various forms of emergency treatment have been recommended but no one of them has proven to be entirely adequate or sufficiently prompt. The first case that we treated with carbon dioxide and oxygen remained in coma for more than two hours after his blood sugar level had been restored to normal and we can properly refer to this case as treatment of protracted coma with carbon dioxide and oxygen. However, after we discovered that the method worked, the second case that we encountered was given carbon dioxide and oxygen when he failed to be aroused from coma within thirty minutes after receiving adequate intravenous injections of glucose. Since that time we have administered carbon dioxide and oxygen to all patients who failed to be aroused within five or ten minutes after adequate injections of glucose. Therefore, it seems proper to refer to this technique as we are now employing it as the prevention of protracted coma by the inhalation of carbon dioxide and oxygen.

Hoch and Kalinowsky[2] report that Muller[3,4] described the use of carbon dioxide for the treatment of protracted shock in 1938. However, in the references given by Hoch and Kalinowsky, Muller does not include carbon dioxide among the treatments which he recommends for protracted shock. There is, however, in one of the references given by Hoch and Kalinowsky, an article by Hadorn[5] in which he describes the use of 5% carbon dioxide and 95% oxygen for the treatment of circulatory collapse occurring during insulin coma. So far as we can determine we are the first to report the use of carbon dioxide and oxygen for the specific treatment and prevention of protracted shock.

Our first experience with this treatment method was the result of a rather unusual set of circumstances. The patient was a forty-five-year-old man who, several years previously, had been discovered to have malignant hypertension. Shortly after the onset of his severe hypertension he had a little stroke. This occurred suddenly one morning while he was shaving. He noticed that he could not move the muscles on the right side of his face and when he attempted to call for his wife he found that he was unable to talk. This facial paralysis and motor aphasia gradually subsided but recurred on several occasions. This was thought to indicate that the patient probably had a thrombosis originally, but that the transient recurrences of his symptoms were due to vasospasms. Eventually, the patient had a thoracolumbar sympathectomy but this did not relieve his hypertension. He was then treated with rauwolfia serpentina with some relief from his hypertension, but while taking this drug he became depressed and was given electroconvulsive therapy. When the patient first came to our attention he was in severe manic excitement, showed transient right sided facial paralyses from time to time and some dysphasia. The severity of the manic excitement justified the risk of electroconvulsive therapy but we could not get permission to use this treatment method. We gave him convulsive carbon dioxide treatments but these relieved his excitement for only a few minutes following each treatment. However, it was observed that his facial weakness and speech difficulty seemed to be improved slightly following each carbon dioxide treatment. In desperation, the patient was started on what was intended to be sub-coma insulin therapy. He was given the usual test doses of insulin over a period of several days and suffered no untoward effects. He was then given forty units of regular insulin at 7:30 one morning. From 7:30 until 9:30 the patient was fairly quiet. There was considerable watery perspiration. At 9:30 he rather suddenly went into deep insulin coma. He had bilateral spontaneous Babinski signs, grasp reflexes were present, pupils were at first dilated then became constricted and did not react to light and his corneal reflexes disappeared. This reaction was so entirely unexpected that at first we found it difficult to believe that the patient could be in insulin coma since he had received only forty units of insulin. However, the seriousness of the situation quickly forced itself upon us. The patient's heart action became irregular and he became cyanotic. We administered oxygen to the patient and gave him intravenous glucose. Instead of coming out of his coma, the coma progressively deepened, and he began to have extensor spasms with abduction

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of the upper extremities indicative of midpontine decerebration. Being familiar with the history indicative of cerebral vasospasm, one of us decided to administer carbon dioxide inhalations on the assumption that his failure to come out of coma might be due to spasm of the cerebral blood vessels. It was decided to use carbon dioxide because this gas is known to be a powerful dilator of cerebral blood vessels. At this point we still found it difficult to believe that the patient's coma had resulted from hypoglycemia. Unfortunately, we did not draw a blood sugar specimen before we administered glucose to this patient and therefore, we will never know how low his blood sugar actually was. It was approximately 11:30 when carbon dioxide was decided upon. The patient was given inhalations of the standard mixture of 30% carbon dioxide and 70% oxygen. Just as he inhaled the twelfth breath of the carbon dioxide mixture he suddenly jumped out of bed and ran off of the ward. This was one of the most dramatic and sudden changes that any of us have ever seen occur in a patient. When the inhalations of the carbon dioxide were begun the patient was a human example of a brainstem preparation in midpontine decerebration. The arousal from the coma was so sudden that the patient caught us by surprise and made his escape. When we finally caught up with him he was disoriented and very excited. In addition to his disorientation and excitement he showed perseveration, rhythmically repeating in a loud voice the word "No-o-o, No-o-o, No-o-o." He was placed in a wet sheet pack and for several hours continued to perseverate in a loud voice, then gradually quieted down and became oriented. Interestingly enough, his manic attack subsided after this episode.

In retrospect there are several interesting speculations about this case. The patient had had a thoracolumbar sympathectomy. Therefore, one of the body defenses against the hypoglycemic action of insulin, namely, the liberation of glycogen stores from the liver and muscles by adrenalin had been put out of action. Lorente de No[6] has shown that the food stuffs stored in the neurons of the central nervous system are sufficient to maintain metabolism for only ninety minutes after a patient becomes hypoglycemic. We can assume that forty units of insulin did make this patient become hypoglycemic at about 8:00 o'clock in the morning. From 8:00 until 9:30 o'clock, the patient presumably utilized the food stuffs stored in the nerve cells. Patients who have not had sympathectomies respond to hypoglycemia by firing off through the sympathetic nervous system with a resulting release of adrenalin. The adrenalin thus released, mobilizes glycogen from liver and muscles and counteracts the hypoglycemia. However, in this patient, this autonomic homeostatic mechanism had been disrupted. This, it seems to us, is at least a plausible explation of this patient's coma in spite of the fact that he only had forty units of insulin. As we look back on this episode, it is seen that the patient became quiet, then drowsy, and that he perspired like any other patient going into a hypoglycemic coma. Therefore, it seems improbable that the coma was related to cerebral vasospasm and that it was in fact, a hypoglycemic coma. Before we can attempt an explanation of the modus operandi of the carbon dioxide administered to this patient, it is necessary that we review briefly something of what is known about the production and utilization of energy by the brain.

The neurons and axones of the central nervous system require energy in order to remain alive, carry out their functions, and maintain the integrity of their structures. It is also likely that the transmission of nervous impulses across synapses requires energy. For all practical purposes it can be considered that almost all of the energy available to the central nervous system is derived from the metabolism of glucose.

The energy requirements of the central nervous system, in the adult human, progressively increase from the medulla to the cerebral cortex. The cortex being phylogenetically one of the newest portions of the brain, has the highest rate of energy consumption and is also the most susceptible to the injurious effects of a decrease in energy production. Proceeding from the cortex toward the medulla, one finds that each succeeding phyletic layer requires less energy than the one above it. The lower one goes in the phyletic hierarchy, the less susceptible is the brain tissue to decreased energy production. Examination of the brains of humans who have died in insulin shock shows more wide-spread destruction in the newer phyletic layers than in the older layers, such as the brain stem and medulla. It is believed that the Embden-Meyerhof cycle is active in the human central nervous system but there is also evidence that methods of glucose oxidation not involving the Embden-Meyerhof cycle may be of greater quantitative importance in brain metabolism.[7] By the Embden-Meyerhof scheme glucose is phosphorylated in the presence of the enzyme glucokinase and the coenzyme adenosine triphosphate, yielding phosphorylated glucose and adenosine diphosphate. The immediate source of energy from this cycle to support nervous functions arises from the breakdown of adenosine triphosphate. Phosphorcreatin is an additional source of energy-rich phosphate bonds which aid in the maintenance of adenosine triphosphate. The energy-rich phosphate bonds may be regarded as playing the role of the middle-man which transfers the energy obtained from carbohydrate oxidation for the support of the brain. The other method of energy production involves the utilization of oxygen in the initial phases of the metabolism of glucose to pyruvic acid. The Kreb's cycle for the oxidation of pyruvic acid to carbon dioxide and water takes place in the same manner irrespective of how the pyruvic acid was formed. During the aerobic metabolism of pyruvic acid the pyruvic acid combines first with carbon dioxide and then phosphate, thus temporarily forming a phosphorylated dicarboxylic acid, (phosphooxalacetate).

These two-carbon residues are fed into Kreb's metabolic cycle in which the first step is the condensation of the two-carbon particles with a four-carbon compound, oxalacetate, to form citrate. The citrate then undergoes a series of reactions which lead to the complete breakdown of the two-carbon particles with regeneration of the oxalacetate. The oxalacetate which is regenerated serves as a cyclic chain reactor or catalyst and it is essential for the perpetuation of the metabolic cycle.[8]

It is believed that this patient, as a result of having received forty units of insulin, exhausted the glucose in his circulating blood and also metabolized the food stuffs stored in his brain cells. Forty units of insulin was able to do this because the patient was unable to mobilize glycogen due to the fact that the sympathetic pathways to his adrenal glands had been severed. The oxalacetate in his brain cells was exhausted and therefore, when we injected glucose into his blood stream the catalytic action of oxalacetate was absent and he was unable to reactivate Kreb's metabolic cycle. However, pyruvate is not exhausted when brain cells are obtaining energy from food stuffs stored within themselves. Therefore, it is assumed that the administration of carbon dioxide to this patient resulted in the condensation of carbon dioxide and pyruvate to form oxalacetate. This is a reaction which is known to occur in the brain. It is further assumed that having been resupplied with oxalacetate the patient was able to reinstitute Kreb's metabolic cycle and metabolize the glucose in his circulating blood.

Another possible explanation of the action of carbon dioxide in terminating protracted shock may be related to the effect of carbon dioxide on potassium transfer. However, we have not done potassium studies on our cases.

A third possible explanation must be considered, namely, the permeability of the blood brain barrier. Forstmeyer[9] has reported that the inhalation of carbon dioxide does cause an increase in the permeability of the blood brain barrier.

The acute excitement that this patient displayed for several hours after termination of the coma can be accounted for in two different ways. The twelve breaths of the gas mixture which he received would constitute what one of us[10] has referred to as a stimulating sub-coma treatment. On the other hand, the fact that he was disoriented and perseverative following the treatment indicates that the higher centers of the brain were not restored to normal functional activity for several hours. This permits us to assume that his excitement can be at least partially explained on the basis of it being a release phenomenon.

The case just cited is, of course, not sufficient to justify the assumptions that have been made but subsequent experience has confirmed our original impressions. Representative examples of our subsequent experiences are outlined briefly below.

The second case of protracted shock occurred in a twenty-one-year-old, white male. This patient had an acute schizophrenic illness. He was very excited, delusional and hallucinating. He was homicidal and suicidal. His severe excitement and homicidal tendencies were only temporarily controlled by a long course of electroconvulsive therapy. Beginning with his fourth insulin coma treatment the patient had a spontaneous grand mal seizure with each treatment until he had received a total of nine treatments. He was very slow to respond to the intravenous glucose which was used to terminate each coma. Daily treatments were continued in spite of his spontaneous grand mal seizures and the slow response to intravenous glucose, because the patient was so disturbed and violent. On the day that the patient developed protracted coma he was given 440 units of regular insulin at 7:12 A.M. He was very restless and active after receiving the insulin and at 9:15 began to have myoclonic twitchings and became very sensitive to external stimulation. At 9:35 he had a spontaneous grand mal seizure. He was given a total of 250 cc. of glucose and his blood sugar was brought up to 140 but instead of coming out of coma, it continued more deeply. Fifteen minutes following the administration of the glucose he was given twenty-five inhalations of 30% carbon dioxide and 70% oxygen. Prior to this he had been given inhalations of pure oxygen without any effect. After breathing the carbon dioxide and oxygen the patient awakened and was able to drink some orange juice but after drinking the juice he relapsed into coma. He was again given twenty-five inhalations of carbon dioxide and oxygen and again he awakened. He was given carbon dioxide inhalations five times between 9:50 and 11:50, remained rather groggy from 11:50 until 2:00 P.M., but after 2:00 P.M. he was completely over the effects of the insulin coma.

Since this patient had been so active and restless during each one of his insulin comas and since he had had spontaneous grand mal seizures during six consecutive comas it is assumed that he probably had exhausted most of the food stuffs stored within the brain cells. With each of his comas he had a sharp rise in systolic blood pressure with a decrease in the diastolic. This is the sort of blood pressure curve that is thought to be indicative of hypersecretion of adrenalin rather than noradrenalin. This outpouring of adrenalin would be expected to deplete stores of glycogen in the liver and muscles. The slowness of this patient to respond to the intravenous glucose used to terminate each of the comas preceding the protracted coma is also in keeping with the assumption that stores of food stuffs were being depleted.

The third case of protracted coma occurred in a forty-two-year-old, white male who had a fairly acute paranoid schizophrenic illness. He was delusional and was hallucinating and was overwhelmed by anxiety. He made repeated serious attempts at suicide. His symptoms were only partially and temporarily relieved by a course of thirty-two electroconvulsive treatments. He was finally given a course of forty-eight insulin coma treatments, eight-

een of which were combined with electroconvulsive therapy. During the initial comas the patient responded rather promptly to intravenous glucose but beginning with the seventeenth coma he began to respond more slowly to the glucose. He was rather restless and had myoclonic twitchings during most of his coma. He improved very little even with the combined insulin coma and electroconvulsive therapy. Therefore, his coma time was gradually increased up to an hour and with the deep coma treatments he did show some slight improvement. Coma was usually terminated by 60 cc. of intravenous glucose although he sometimes required 90 cc. During the week preceding the protracted coma, the patient was permitted to remain in coma 68-70-80-85-96 minutes respectively.

On the day of the protracted coma the patient was given 120 units of regular insulin at 7:05 A.M. At 10:00 A.M. he rather suddenly went into very deep coma with extensor spasms. He was given a total of 370 cc. of intravenous glucose but could not be aroused. In fact, his coma continued to deepen in spite of the administration of glucose. Inhalations of 30% carbon dioxide, 70% oxygen were begun, but it was only after breathing about 100 inhalations that the patient came out of coma. When he did come out of coma, his sensorium was quite clear and he seemed more normal than at any time during his hospitalization. However, he relapsed into coma a few minutes after the carbon dioxide was discontinued. The inhalations of carbon dioxide were repeated six times during the next two hours and each time we gave him carbon dioxide he came out of, then relapsed back into coma. However, after the sixth administration of carbon dioxide he remained alert and was able to take nourishment.

This patient was relatively quiet while in protracted coma and his pupils were dilated (he had received atropine as pre-treatment medication). Therefore, we were able to get a good look at his eyegrounds. Each time he went into coma his retinal arteries constricted and each time we gave him carbon dioxide these vessels dilated. After he ceased to relapse into coma there was no longer any constriction of his retinal arteries. Whether or not this is significant we do not know.

In addition to the use of carbon dioxide for the termination of resistant or protracted coma we have used carbon dioxide to quiet the excitement that some patients undergo while going into or coming out of insulin coma. Some patients become very active and hypersensitive to stimuli as they're going into insulin coma. During these periods of excitement tendon reflexes are hyperactive, there is generalized myoclonic twitching and sometimes grand mal seizures occur. The administration of pure oxygen to these patients sometimes will quiet them but it is usually necessary to have them breathe the oxygen for as long as ten to twenty minutes. However, if they are given 30% carbon dioxide and 70% oxygen the excitement and myoclonic activity can be frequently controlled with not more than twenty-five inhalations of the gas mixture. All patients do not respond to this form of treatment, but when it does work it is so dramatic that we find it useful to keep carbon dioxide on hand in the insulin treatment ward. The inhalations of carbon dioxide during the excitement stage do not completely arouse the patient from coma but there usually is a lightening of the coma to the point that he can be reassured by the physician or attendant. If the inhalation of carbon dioxide does quiet the patient he will then usually go into a satisfactory coma without the recurrence of myoclonic activity or excitement.

Certain patients become highly excited and agitated as they awaken from comas following the intravenous administration of glucose. Sometimes they become so excited and violent that the cardiovascular system is adversely influenced. One of our patients in such a state of agitation developed ventricular fibrilation with a fatal outcome. Some patients are dramatically relieved of this excitement by the inhalation of carbon dioxide. However, other patients are not quieted thereby. If severely excited patients are not quieted by fifty inhalations of 30% carbon dioxide and 70% oxygen we believe it advisable to give paraldehyde intramuscularly rather than attempt prolonged inhalations of carbon dioxide. Prolonged carbon dioxide inhalation in such cases is likely to result in a carbon dioxide convulsion.

*Summary*

We have reported three cases of protracted insulin coma which responded to inhalations of a mixture of carbon dioxide and oxygen. We have postulated that the carbon dioxide terminates these resistant comas by restoring oxidative metabolism in the brain.

We have also reported upon the use of carbon dioxide for quieting certain excitements that some patients undergo while going into or coming out of insulin coma. These excitements are thought to be release phenomena and the ability of carbon dioxide to quiet them in certain instances is thought to be due to an enhancement of oxidative metabolism brought about by the carbon dioxide. It is believed that the carbon dioxide restores cortical functioning and that the cortex is then able to exert its inhibiting effect upon the diencephalon and perhaps other subcortical structures.

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# Factor of Aggression as Related to the Electroencephalogram

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During the past two years an intensive study has been made of the relationship between the psychological factors in personality structure and the characteristics of the electroencephalogram (EEG). This study was undertaken because of a mass of previous evidence demonstrating that the EEG's of persons with psychological disorders showed in general, different patterns from those of normal individuals.[7] In two previous publications resulting from the first year's work by the above authors and their many aides, it was shown that the basic EEG pattern as analysed by various wave-frequency relationships, has definite correlation both with psychiatric diagnostic criteria and with psychological attributes. In particular the factor of anxiety, as determined by psychological tests, was shown to relate to fast EEG frequencies and to variability of pattern.[8,10]

In the study reported here, the factor of aggression or of acting-out hostility, has been examined, using similar methods of analysis. This quality was of special interest because of the evidence of others that a low frustration level is directly related to an unusual amount of theta activity, the 4-7 per second wave-form of the EEG.[2,4,9] Theta activity appears in normal records to some degree and is most frequent normally in late adolescence where it is considered as a transition form during maturation.[4] This is also the particular age wherein intolerance, easy rage and fighting tendencies are most common.

Theta activity in abnormal amounts also appears in relation to easy rages. Hill and his associates[4,5] first recognized this. They noted further that theta activity appeared in many cases of psychomotor epilepsy, a clinical condition known to be related to rage paroxysms and that in such instances it appeared chiefly or entirely in the temporal cortex. It is now common knowledge that surgical removal of such foci have, in many instances, abolished the symptoms of psychomotor rage as well as the abnormal EEG focus.[1]

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*Method*

The present report is based on the findings of 192 subjects who have had both EEG's and psychological tests once or several times during the past two years. All were between the ages of 12 and 30. None had shown evidence from either history or tests of any focal organic lesion of the nervous system. The 50 control subjects were members of the nursing, dietetic or office staff at either the Provincial Mental Hospital at Essondale, B.C., or at the University of British Columbia. Thirty-three others were inmates of a prison colony and largely psychopaths. The remaining 109 cases were all patients in the above mental hospital. No subject was included who had an I.Q. below 80. An attempt was made to match the individuals within the groups for age, sex, and educational achievement.

The psychological tests routinely given were: Rorschach, Wechsler-Bellevue and Bender-Gestalt. These were supplemented when indicated by other tests. The usual routine estimates were made from the accumulated psychological data. In addition, patients were rated for hostility and for anxiety according to the following criteria.

Specific indices on each of the three tests were utilized to formulate a picture of personality structure where the dynamic mechanisms could be inferred, i.e. to what extent feelings of hostility and anxiety were contributing to the total personality picture. (Discussion of the indices as tools in objective personality assessment will be given in a paper to follow.) These assessments are composites, i.e. these feelings are not exclusive—the anxious may be passive or hostile, etc. Where one factor—anxiety for example—(a) dominated the entire picture of personality structure (b) rated highly in comparison to others, that individual was placed in the "anxiety" category. Patients who have been listed in these categories may therefore be considered as taking points towards the extreme ends of a hostility gradient, passivity gradient and anxiety gradient.

## TABLE I

*Subjects Examined During Present Survey*

| | AGES | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 12-15 | | | 16-20 | | | 21-25 | | | 26-30 | | | 12-30 | | |
| | M | F | All | M | F | All | M | F | All | M | F | All | M | F | All |
| Mental Hospital | | | | | | | | | | | | | | | |
| 1st year | 0 | 0 | 0 | 3 | 8 | 11 | 6 | 6 | 12 | 13 | 8 | 21 | 22 | 22 | 44 |
| 2nd year | 3 | 4 | 7 | 8 | 3 | 11 | 11 | 9 | 20 | 10 | 17 | 27 | 32 | 33 | 65 |
| Total | 3 | 4 | 7 | 11 | 11 | 22 | 17 | 15 | 32 | 23 | 25 | 48 | 54 | 55 | 109 |
| Prison Colony | 0 | 0 | 0 | 7 | 5 | 12 | 11 | 1 | 12 | 9 | 0 | 9 | 27 | 6 | 33 |
| Normal Controls | 0 | 0 | 0 | 4 | 16 | 20 | 11 | 6 | 17 | 7 | 6 | 13 | 22 | 28 | 50 |
| Total | 3 | 4 | 7 | 22 | 32 | 54 | 39 | 22 | 61 | 39 | 31 | 70 | 103 | 89 | 192 |

## TABLE II

*Bender Gestalt as Related to Age and Sex*

| | Menta Hosp. | | Prison | | Controls | |
|---|---|---|---|---|---|---|
| | Mean | Var. | Mean | Var. | Mean | Var. |
| Males | 89.1 | 56-135 | 68.3 | 44-97 | 57.4 | 41-75 |
| Females | 86.5 | 64-165 | 61.7 | 44-80 | 54.4 | 37-79 |
| Both Sexes | 87.6 | 56-165 | 67.2 | 44-97 | 55.7 | 37-79 |
| Ages 12-15 | 91.4 | 74-116 | — | — | — | — |
| 16-20 | 88.2 | 65-125 | 67.6 | 44-93 | 57.9 | 41-79 |
| 21-25 | 89.1 | 56-125 | 66.5 | 50-97 | 52.5 | 37-70 |
| 26-30 | 86.1 | 64-165 | 56.0 | 50-80 | 55.2 | 41-67 |
| All Ages | 87.6 | 56-165 | 67.3 | 44-97 | 55.7 | 37-79 |

The EEG's were recorded in a routine fashion on a Grass eight-channel machine. The frequency analysis was made by use of an Offner instrument. The details of the procedure are reported elsewhere.[8] The pen of the frequency analyser records the total voltage or energy utilized in each of a series of wave-rates from 4 to 30 per second. A graph was then made from each record by measuring the total energy within a ten-second epoch, or height of displacement of the analyser pen, for each frequency and for each of the eight cortical regions from which frequency analysis had been made (Fig. 1). After several hundred of these graphs had been examined, significant factors in which individual differences occurred were selected and were then arranged in terms of the frequency of their occurrence in the group of fifty normal controls. These constitute the abscissae of the accompanying charts. Thus, on the left side, good organization and high alpha activity indicate a normal pattern and on the righ poor organization and left-right dyssynchrony are part of abnormal disorganization.

The 127 subjects and their data presented in the previous papers have been utilized here in the study of aggression. The 65 patients examined during the second year have been added. Forty of this latter group have had repeated EEG's and psychological tests in a longitudinal study to be reported elsewhere.

### *Data*

Table I gives the data for the total number of 192 subjects. It will be seen that there are seven under the age of 16. These entered the survey because during the second year a change in policy in the mental hospital lowered the age of admission. In Table II the Bender-Gestalt findings have been related to age and sex in an examination of the entire 192 subjects. It will be seen that there is no difference in Gestalt distribution between the sexes but that there is a slight and consistent rise in average scores, progressing from oldest to youngest age group. This difference is not, however, statistically

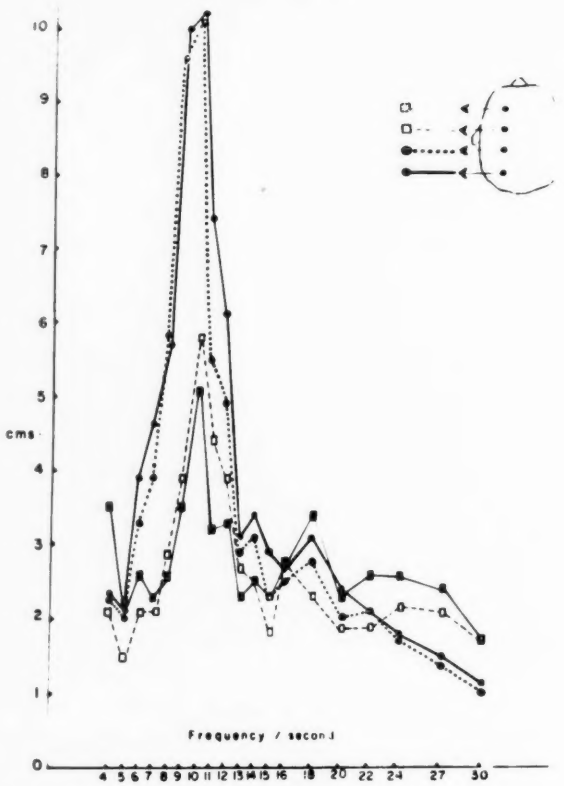


*Figure 1.* Graph illustrating frequency pattern of EEG from left side of head recorded by frequency analyser.

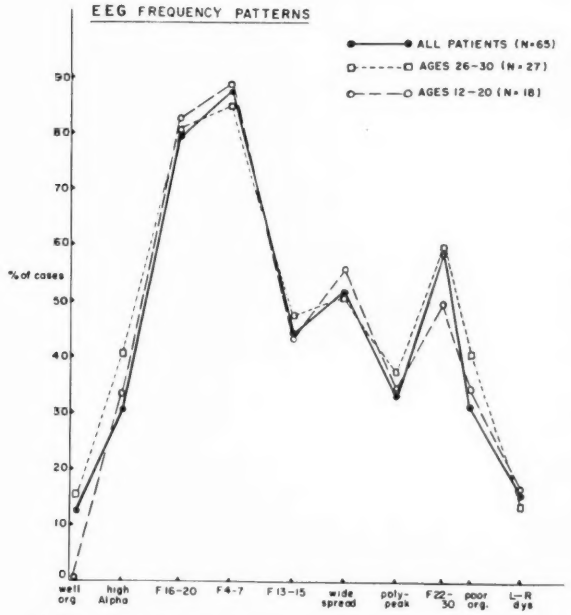


*Figure 2.* EEG frequency patterns illustrating absence of effect of age within the survey.

significant and no previous findings have been reported showing age differentiation. It will be seen, however, that average scores and distribution for the three groups, patients, prisoners and controls, are quite different; that of the normals being 55, of the prison inmates 67 and of the mental hospital patients 87. These figures are consistent with the findings of those who have established and stabilized the Gestalt test and its scoring.[3,10] Figure 2 shows the average EEG frequency profile of the last 65 consecutive patients examined, and compares age groups. There is no difference between that of the 27 patients ages 26-30, that of the 18 patients ages 12-20 and that of the total 65.

At the end of the first year, while scanning the various psychological factors for comparison with EEG patterns, an unexpectedly high correlation was found between a low frustration threshold and a high or abnormal score on the Bender-Gestalt test. When the two groups having high and low Gestalt scores were then compared as to EEG analyser profiles a positive correlation also appears (Fig. 3). It will be seen that the frequency spectra of these two groups differ only in the criteria related to theta activity at 4-7 per second and in the faster waveform at 13-15 per second which frequently accompanied it. Because of these findings, greater effort toward analysis of the factor of aggression has been made during recent months and the remaining data in this paper are based on analysis of these 65 subjects, all patients in the mental hospital.

The 65 patients were first classified according to the discharge diagnoses made by the clinical physicians. Table III shows the findings as related to Gestalt scores for the four diagnoses found to show different scores, those of the schizophrenic and anxiety states being somewhat above that of the average of 87.6 for the 65 patients, and those of the psychopath and sex offender being very far below this average and more nearly like that of the inmates of the penitentiary. In Figure IV which shows the frequency profile of the two extremes, that of schizophrenic and anxiety state being grouped together and that of psychopath and sex offender, it can be seen that the profile of the higher Gestalt groups is less normal than that of the lower. But in this graph statistical significance appears only in relation to differences in 13-15 per second activity and in that of disordered alpha, the latter being only at the 5% level.

Table III gives also the Gestalt data of two groups, which have been defined according to psychological characteristics. Of the 65 mental hospital patients there were 34 showing marked anx-

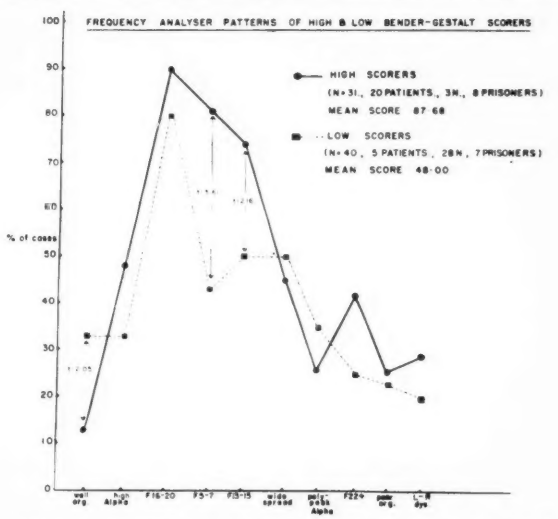


*Figure 3.* EEG frequency patterns of 31 high scorers and 40 low scorers in Bender-Gestalt test, showing significant differences in theta pattern between the two groups.

## TABLE III

*Bender-Gestalt as Related to Psychological and Psychiatric Criteria*
*Sixty-Five Patients*

| | No. | Mean | Var. |
|---|---|---|---|
| Schizophrenia | 26 | 85.1 | 65-110 |
| Anxiety-Neurosis | 13 | 89.6 | 66-165 |
| Psychopaths | 15 | 79.9 | 56-121 |
| Sex-Psychopaths | 8 | 70.8 | 60-86 |
| Hostility | 17 | 93.0 | 65-117 |
| Anxiety | 34 | 92.4 | 56-125 |

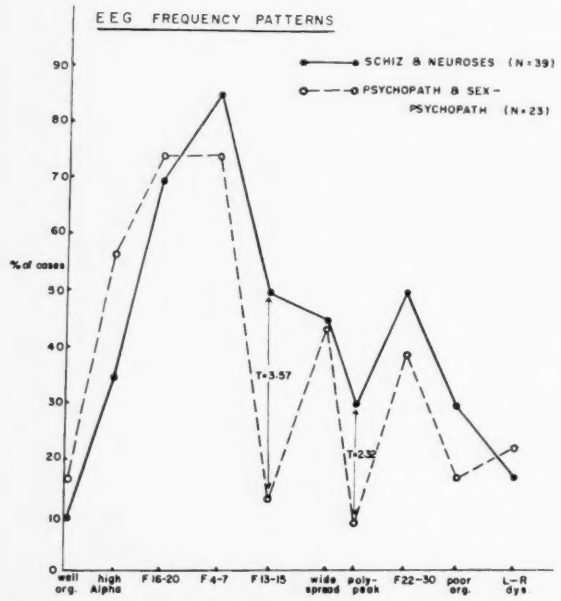


*Figure 4.* EEG frequency pattern comparing clinical diagnoses and showing significant differences between the schizophrenics and neurotics as compared with the psychopaths.

iety and 17 with marked hostility. The average Gestalt scores are respectively 93.0 and 92.4 for these two groups. Their EEG profiles (Fig. 5) are slightly less normal than that of the total 65. These differences are not, however, of statistical significance in the numbers used in the present group.

Finally, in Figure 6, a comparison is made of the EEG profiles of those 13 patients having a Gestalt score of 70 or less with those 17 patients having a Gestalt score of 100 or more. The EEG pattern of the high scrorers is definitely more abnormal than that of the low scorers, just as it was in Figure 2 which utilized a different group of subjects. In Figure 6, in which all subjects are mental patients, alpha activity is definitely higher in the low scorers, but in all other criteria where there is a difference, the high Gestalt scorers have less normal frequency patterns. In this Figure at the right is shown the percent of subjects in each Gestalt group who had been found to have either anxiety or hostility. There is a marked difference. Of the 17 patients having an abnormal Bender-Gestalt score, above 100, 41 percent had indications of hostility and 54 percent of anxiety in their psychological appraisals, while of those 13 subjects having low scores only 8 percent showed hositlity and 25 percent anxiety.

*Discussion*

From these data it is felt that additional information has been attained which indicates that the EEG patterns which occur among subjects with unstable or abnormal personalities can be related in accurate detail to specific factors of psychological import. Thus the earlier observations of other investigators, dating as far back as those of Pauline Davis in 1937[12] are confirmed and, in addition, the possibility of utilizing the EEG pattern as a more specific diagnostic aide becomes more certain.

In the present study, hostility as measured by psychological tests has been found to relate to theta activity as measured by frequency analysis, and both qualities relate significantly to a high or abnormal Bender-Gestalt score, when measured in a

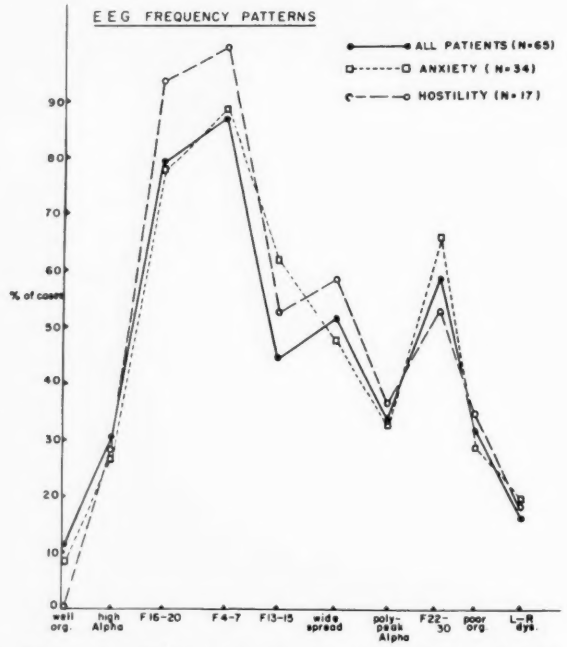


*Figure 5.* EEG frequency pattern of 34 patients showing anxiety and 17 patients showing hostility as indicated in psychological examinations. Slight differences between these groups and the average for 65 mental hospital patients.

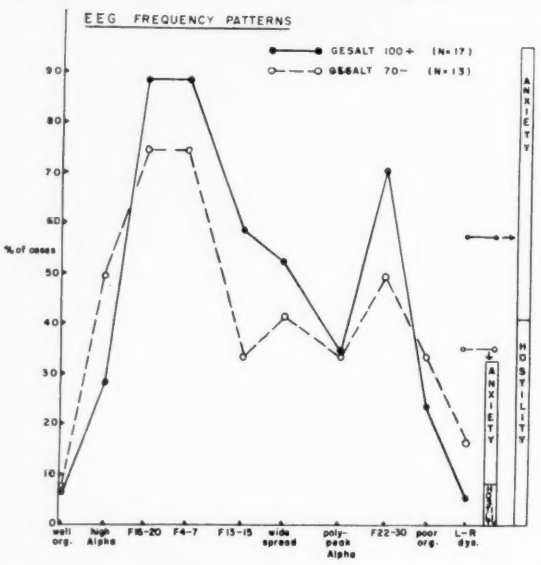


*Figure 6.* EEG frequency pattern comparing 17 individuals with high and 13 individuals with low Bender-Gestalt. Very marked differences appear between the two groups in the correlation of anxiety and hostility as well as in EEG correlation.

group of mental hospital patients (Fig. 6) and in a group (Fig. 3) containing the high scorers of both mental patients and prison inmates. Further examination of the data reveals that those cases which tend to have high theta activity are also those having a high increment of the wave-forms at 16-20 per second and, more especially, at 22-30 per second. The latter, faster wave-form is that shown previously to relate to anxiety as measured by psychological tests. In this series 12 of the 17 cases rated as showing hostility were also in the list of 34 cases showing marked anxiety (Fig. 5). It is of interest that all of these cases were severely disturbed, certainly more so than the average of the series; 8 having a diagnosis of schizophrenia, 2 of anxiety-neurosis and 2 of immaturity and behaviour disorder. The average Gestalt score for the 12 is 96.5 and the range of scores, 65 to 135, actually the highest average found in any group which we have differentiated.

The meaning of the Gestalt abnormality as related to hostility has been one which has received much consideration but which remained obscure until further investigation in the two-year series disclosed the fact that those individuals having the high Gestalt test were also those having high anxiety as well as hostility. The total personality structure of the individual having high Gestalt, high anxiety and/or hostility and a high incidence of EEG frequencies of abnormal range becomes, then, that of the individual who is less stable and more pervious to disturbances by his environment. There is some indication that as a patient in a mental hospital he is more seriously and deeply upset for these are the schizophrenics, the group with high anxiety quotients, and the young and unstable disorders of behavior. On the other side lies the individual who has relatively normal psychological qualities as related to his inner stability. His EEG pattern likewise is more like that of the normal. These individuals, the psychopaths and the sex offenders, are far less pervious to the alarming signals from their environment and, indeed, by virtue of their steady state, are often in difficulty because of a complete disregard of the implications of this environment in relation to themselves.

### *Conclusions*

In a study of the relationship of personality structure to electroencephalographic characteristics, the factor of aggression or of low frustration threshold has been examined in 192 young individuals from (1) a mental hospital, (2) a prison colony and (3) a normal control group, with the following results:

1. Hostility or "acting-out aggression" appears to be positively related to EEG theta activity in this study as in previous ones of other investigators.
2. Both hostility and EEG theta activity show a positive correlation with a high and therefore abnormal score on the Bender-Gestalt test.
3. Clinical diagnoses and data from other psychological tests, notably the Rorschach, indicate that the factor of low frustration level is part of a generalized relatively unstable, fluctuant and severely disturbed personality, and that the EEG pattern of this group is similarly fluctuant, unstable, and poorly organized as compared with that of the normal controls and of the psychopaths who are relatively stable with respect to their environment.

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# The Grantham Lobotomy for the Relief of Neurotic Suffering

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Neurotic suffering is symptomatic of a variety of psychiatric disorders in which the personality of the patient is relatively intact even after years of illness. It may be due to persistent anxiety or depression, agonizing obsessions, recurrent doubts, irresistible compulsions, or torturing phobias. The primary cause of neurotic suffering often is irremediable and the resistance of these disorders to the usual method of psychiatric treatment is well known. In these cases, therefore, relief from neurotic suffering becomes the prime objective of treatment.

The relief from neurotic suffering that can be obtained by adequate psychosurgery is well recognized. However, psychosurgery for this purpose has seldom been employed in patients with fairly well preserved personalities, because of the personality changes, intellectual deficits, and convulsions that may follow the standard lobotomy operations.

In 1951, Grantham announced a new method of selective destruction of the ventromedial quadrant of the prefrontal lobe by electrocoagulation which eliminated many of the undesirable effects of the standard lobotomy procedure.[1] Intially, Grantham performed his operation for the relief of pain in cancer patients. He observed the most beneficial results in those patients in whom anxiety was predominant. Since then, he has operated on approximately 200 psychiatric patients with some excellent results.[2] McIntyre, Mayfield and McIntyre, in 1954, reported their favorable experience with the Grantham lobotomy in 30 psychotic and neurotic patients.[3] These preliminary reports suggested that the Grantham lobotomy was superior to conventional psychosurgery for the relief of neurotic suffering.

### *Clinical Material*

To evaluate the therapeutic effectiveness and advantages of the Grantham lobotomy this operation was performed on 30 non-hospitalized patients ranging in age from 24 to 75. These patients were severe, chronic neurotics or psychotics in whom neurotic symptomatology was paramount. All were seriously incapacitated by illnesses of three to 30 years' duration. Their illnesses had been refractory to one or more of the following therapies: psychotherapy, group therapy, psychoanalysis, insulin and electro-shock, subcoma insulin, and hospitalization. In addition these paientts had not benefited from Thorazine (300 mgm to 800 mgm daily) or Serpasil (3 mgm to 10 mgm daily) which they received for a period of two months to one year. Included in this group were 12 chronic mixed psychoneuroses, five chronic obsessive-compulsive neuroses, nine involutional depressions, two pseudo-neurotic schizophrenias, one paranoid schizophrenia, and one catatonic schizophrenia.

### *Selection of Patients*

In the selection of patients for psychosurgery three factors are important: (a) the degree of anxiety and its incapacitating effects, (b) its intractability, and (c) the intactness of the personality. In view of the gravity of the decision to be made, in addition to repeated psychiatric examinations, special tests such as Rorschach and Funkenstein shuold be done whenever possible. If these preoperative investigative procedures disclose severe anxity or depression, the patient is considered a proper candidate for lobotomy, providing there are no associated serious psychopathic traits.

A. *Psychoneuroses:* Twelve chronic psychoneurotic patients in this study suffered primarily from anxiety which was expressed in a variety of ways. They complained of persistent tension and apprehension, easy fatigability, feelings of inadequacy and inferiority, inability to concentrate, fear of insanity or some disease such as cancer, irritability, insomnia, crying spells, and depression. They suffered from repeated alarming anxiety attacks and psychosomatic disturbances. For years these patients sought relief from their symptoms by frequent visits to general practitioners, internists, and psychiatrists. In a fruitless search for a physical cause for their symptoms they had repeated cardiograms, x-rays, and other laboratory tests. Some were hospitalized at least once for surgery. They tried innumerable drugs, hypnosis, psychotherapy, psychoanalysis and in a few cases shock therapy. Because they had not responded to any previous treatment and permanent disability seemed inevitable, these patients were considered apt candidates for the Grantham lobotomy.

B. *Obsessional Neurosis:* No two obsessive-compulsive patients are alike. Therefore, obsessional patients must be carefully assessed for psychosurgery. In this study there were five intensely anxious obsessional neurotics whose distress was due primarily to obsessional thinking and phobias rather than to irresistible compulsions. They were tortured by recurring thoughts of harming someone. They suffered with religious scruples. Fears of every sort haunted them. They lived in constant doubt and had to go over things again and again. Frequently, they could not cope with the ordinary stresses and vicissitudes of life. Although they dreaded insanity and commitment to a psychiatric

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institution, they often asked if it was safe for them to live outside of a hospital. They were chosen for modified psychosurgery because they had not been helped by years of psychotherapy and psychoanalysis and there was no hope for a spontaneous remission.

C. *Depressive States:* Different varieties of depressive reactions may occur in the involutional period. Those which occur in the chronically anxious patients are characterized by intense anxiety and depression. These patients frequently are made worse by electroconvulsive therapy which relieves the depression but causes mounting anxiety and agitation. Many of these patients recover from their depressed state with conservative treatment. In some patients, however, the anxious depression becomes chronic.

In this study there were seven chronically anxious patients who became depressed during the involutional period. They complained of hot flushes, dizziness, headaches, rapid heart, indigestion, anorexia, constipation, and insomnia. Their mood was anxious and depressed and crying spells were frequent. They were sensitive and troubled by feelings of guilt, remorse, and unreality. They lacked confidence. They had no interest in their usual pursuits and thought of suicide. ECT had been administered to five of these patients. One patient had had 90 shock treatments and another over 200 treatments. All feared shock therapy because it made them so anxious. Because these patients had not responded to ECT, hospitalization, and other psychiatric treatment, they were selected for a modified lobotomy.

The effectiveness of ECT for involutional depression is well documented. However, there are some involutional depressives who respond initially to ECT but subsequently relapse. In these patients repeated convulsive treatments produce a transient elevation of the mood but no change in their melancholic ideation. In this study there were two chronic involutional depressives, who had not responded to repeated courses of ECT. They complained of unrelenting feelings of despondency and disinterest in anything but themselves. They spoke continuously of how they felt. They were self-deprecatory and self-derogatory. Hence they were selected for modified psychosurgery.

D. *Schizophrenic Reactions:* In this study, modified psychosurgery was considered for those schizophrenic patients who were not deteriorated. These patients were more disabled by the intensity of their neurotic suffering than by delusions and hallucinations.

*Technique*

Bilateral burr holes are made in the frontal area 6 to 8 cm. from the glabella and 2½ cm. lateral to the midline. The frontal horn of each lateral ventricle is injected with 10 cc. of air. Insulated electrodes are inserted into the frontal lobe parallel to the sagittal sinus and anterior to the frontal horn of the lateral ventricle until they contact the floor of the skull. The electrodes are then withdrawn 2 cm. and their position checked by lateral and anteroposterior roentgenograms. If the electrodes are not parallel or if the tip of either electrode is not in the correct position in the ventromedial quadrant, they are reinserted until their proper position is confirmed by x-ray. Electrocoagulation is then performed by turning on the current for 30 seconds at position 10 on the Universal Bovie electro-surgical unit.

*Post-Operative Course*

A. *Surgical:* In the immediate post-operative period (24 to 72 hours) most patients run a slight elevation of temperature up to 102 degrees. This rise of temperature is important prognostically since it occurred in most of the patients with a favorable therapeutic result. The majority of those patients with slight or no improvement did not have a post-operative elevation of temperature.

There are no marked variations in pulse or blood pressure following the Grantham operation. Improved patients had a decrease in their basal blood pressure of 10 to 20 mm. Hg. which begins to return to the pre-operative level after four to six months.

Post-lobotomy convulsions have not occurred in this group of patients. One man had a severe post-operative infection with meningitis. One woman hemorrhaged on the operating table but her post-operative course was uneventful. Most individuals were ambulatory 48 hours post-operatively. All but five patients were discharged from the hospital on the third to the fifth post-operative day.

B. *Psychiatric:* After recovery from the anesthetic most patients are mentally alert, and usually the benefits of the operation are apparent immediately. Psychiatric examination on the second and third post-operative day reveals an absence of confusion, disorientation, and retrograde amnesia, permitting an early evaluation of the patient's mental state. Impressive relief from anxiety and depression is observed in improved patients, while little or no change can be detected in those who are unimproved. Only one patient who appeared improved in the immediate post-operative period subsequently relapsed. All the others maintained their initial improvement for the six months to one year follow-up period.

A mild euphoric reaction occurred in two women. This euphoria appeared on the second post-operative day and subsided without special treatment within a week. A delirioid reaction occurred on the third post-operative day in two men who had been receiving barbiturates for several months prior to surgery. The clinical picture in these two cases closely resembled barbiturate withdrawal. Recovery from this delirioid reaction occurred within two weeks.

In this series of patients no serious adverse personality changes occurred. There was no release of undesirable neurotic or psychopathic traits. One elderly woman became more critical of, and hostile toward a relative with whom she has never had satisfactory interpersonal relations. Another elderly woman was quite irritable and argumenta-

tive, but this was controlled by Thorazine. Inertia, apathy, abnormal behavior, overtalkativeness, outspokenness, lack of initiative, wetting, excessive appetite, and loss of sexual control or moral inhibition did not occur in any of these patients.

*Therapeutic Results*

*A Definition of Terms:* 1—Marked improvement indicates dramatic relief of neurotic suffering, especially anxiety or depression. These patients were greatly improved over the pre-operative level, being abl to cope adequately with situations which formerly evoked intense emotional reactions.

2—Moderate improvement means that there was less spectacular relief of neurotic suffering. These patients still have some neurotic symptoms, but they concern the patient less.

3—Slight improvement signifies some reduction in tension. Otherwise, these patients are essentially the same as pre-operatively.

4. Unimproved indicates that the patient derived no benefit from surgery.

The Grantham lobotomy produced marked improvement in 18 patients, moderate improvement in six, and slight improvement in two. Four patients were unimproved (Table I). This high rate of improvement is partially due to the selection of only the most suitable candidates for the operation.

*Rorschach Studies*

A pre-operative Rorschach was administered to 22 patients. In general, these tests revealed the effects of prolonged anxiety in the retention of rigid intellectual controls with a resultant decline in spontaneity. Except for the obsessive-compulsives, who expressed their anxiety in a ceaseless striving for quantity, their productivity was below that of the normal. Their thinking was stereotyped and perseverative. They were prone to make hasty generalizations with inadequate articulation of the stimulus. They were unable to delay their impulses to allow them to engage in creative inner living. A weakening of control in the affective realm rendered them highly irritable but lacking in capacity for genuine emotional rapport. The Rorschach pattern did not disclose any positive signs for predicting the clinical outcome.

*Funkenstein Test*

Pre- and post-operative Funkenstein tests were performed on 21 patients. Pre-operatively 16 patients were in Groups VI and VII, four in Group I, and one in Group IV. The physiologic reaction of these patients to Mecholyl was moderate to marked. Epinephrine precipitable anxiety occurred in eight patients.

One month post-operatively, the Funkenstein tests revealed a mean fall in the basal blood pressure of 13 mm Hg. The physiologic reactions of these patients to Mecholyl were more normal. Six of the eight paietnts with epinephrine precipitable anxiety pre-operatively, had the same reaction post-operatively. Thirteen of the 16 patients in Groups VI and VII pre-operatively fell into Group II or III post-operatively. Two other Group VI patients were in Group I post-operatively. Two of the four patients in Group I were in Group III after lobotomy. The remaining patients were in the same Funkenstein group pre-and post-operatively.

*Advantages of Grantham Lobotomy*

There are many advantages to the Grantham lobotomy which make this operation superior to conventional psychosurgery for neurotic suffering. This operation causes little destrucstion of the cortex. The lesion produced in the ventromedial quadrant is relatively small in contrast to the extensive area of destruction caused by conventional psychosurgery. This minimal damage to the cortex and the limited subcortical lesion substantially reduce the hazard of post-operative personality changes and convulsions.

Since the lesion in the ventromedial quadrant is small, it may not transact all of the fronto-thalamic fibers. The patient may only partially benefit from the operation. If necessary, therefore, the operative lesion may be enlarged by a second or third operation. Two patients in this study were unimproved after the first Grantham lobotomy. A second operation produced moderate improvement in one and slight improvement in the other.

Ventromedial quadrant electrocoagulation places little stress upon the patient's physical constitution. Physical disorders which would make conventional psychosurgery hazardous are not a contraindication to the Grantham lobotomy. The patients in this study had a variety of cardiovascular and pulmonary diseases which did not increase the operative risk.

Psychosurgery is not a procedure of last resort. It is a part of the total therapeutic program. It should be followed by psychotherapy and other rehabilitative measures. The rapidity with which a patient recovers from the Grantham operation, along with the absence of the psychic disturbances that follow standard lobotomy permits the initiation of psychotherapy and rehabilitation in the immediate post-operative period. This is a decided advantage over other forms of psychosurgery.

Since the Grantham lobotomy usually does not cause personality changes and the recovery period is so rapid, lengthy hospitalization and special nursing care is unnecessary. The patients herein reported were in ward beds. The majority were am-

TABLE I
THERAPEUTIC RESULTS

| | Marked | Moderate | Slight | Unimproved |
|---|---|---|---|---|
| *Diagnosis* | | | | |
| Psychoneurosis, Mixed | 7 | 4 | | 1 |
| Obsessional Neurosis | 1 | 1 | 1 | 2 |
| Involutional Anxious Depression | 7 | | | |
| *Schizophrenia* | | | | |
| Pseudo-Neurotic | 1 | | | 1 |
| Paranoid | 1 | | | |
| Catatonic | | | 1 | |
| TOTAL | 18 | 6 | 2 | 4 |

bulatory on the second or third post-operative day and were well able to tend to their personal needs. All but five patients were discharged from the hospital on the third to the fifth post-operative day. These factors make the Grantham operation economical, a consideration of prime importance to the private patient whose finances have been depleted by an expensive chronic illness.

This operation does not create any serious cosmetic problems, especially for the women. The operative scar is just behind the hair line. After the bandages have been removed, the women can conveniently cover the shaved area by rearranging their hair style. For the female patient this is of the utmost importance. In this study the women were not self-conscious about their appearance and this encouraged early socialization.

*Summary*

Thirty chronic neurotic and psychotic patients in whom neurotic suffering was paramount have been treated by the Grantham lobotomy. Pre-operatively, these patients had been refractory to the usual methods of psychiatric treatment. The Grantham operation produced marked improvement in 18 patients, moderate improvement in six, and slight improvement in two. Four were unimproved.

This paper covers the selection of patients, the post-operative course, and the advantages of this psychosurgical procedure. It indicates that the Grantham lobotomy is a tremendous step forward in the treatment of neurotic suffering.

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# Experimental Catatonia in Animals and Induced Catatonic Stupor in Man

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I. *Experimental Catatonia in Animals:*

Experimental catatonia with bulbocapnine in animals was first described by the author and Baruk in 1930.[1] Preliminary experiments with bulbocapnine have been made by the author since 1921. In collaboration with Baruk[1] we set up the syndrome of Experimental Catatonia produced by bulbocapnine consisting of:

(A) Hypokinetic, (B) Hyperkinetic, and (C) Autonomic phenomena.[1,2]

(A) HYPOKINETIC PSYCHOMOTOR PHENOMENON

1. Diminished motor initiative, i.e., the impulse to movements and acts is diminished.

2. Catalepsy. The animal assumes positions passively introduced by the examiner.

3. Negativism. A physiological phenomenon consisting of passive and active resistance to changes of positions already assumed.

(B) HYPERKINETIC PSYCHOMOTOR PHENOMENA

We are dealing here with an abundance of movements, such as running, jumping, etc. This is the equivalent of catatonic excitement.

(C) AUTONOMIC PHENOMENA

Salivation, polypnea, vasomotor symptoms, etc.

For further details see the books published in 1930 by the author with Baruk[1] and in 1945 by the author.[2]

In bulbocapnine-catatonia there is predominance of catalepsy over negativism. An experimental picture in animals in which there is predominance of negativism over catalepsy is given by mescaline as was first described by the author in 1930. Moreover, other experimenters, at first Beringer,[4] have described in men a state resembling a psychosis with marked hallucinations and thought disorders, together with autonomic signs such as vomiting, salivation, and mydriasis.

When we combine the findings of former investigators in men with my results with higher dosages in higher animals we come to the conclusion, that mescaline is capable of producing a psychophysiological parallelism, consisting of thought disorders, hallucinations, autonomic phenomena and psychomotor symptoms of a type of experimental catatonia, in which physiological negativism predominates over catalepsy. In dementia praecox the same group of symptoms may occur.[2,3] All in all, it could be that the combined mescaline picture is very much related to dementia praecox; however, it may be more cautious to state as I did for the first time, that there is a marked similarity in the principle of the triad of groups occurring in dementia praecox and mescaline intoxication. The same is true for LSD intoxication which also produces bulbocapnine-like signs in animals.

One of our first reflections was whether or not it would be possible to find "the catatonizing chemical nucleus," starting out with mescaline and trying to reduce the chemical formula more and more.

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With the help of several collaborators we finally found that nitrogen itself may produce catatonic phenomena. Then the question arose, is it nitrogen that acts chemically catatonizing or is it the state of asphyxiation? It proved to be the latter. $CO_2$, hydrogen, oxygen lack in general, proved to be capable of producing the phenomena of experimental catatonia. Our hypothesis was that cellular oxygen-lack might be the common denominator in the different ways, detected later, to produce experimental catatonia.

The ways other than bulbocapnine to produce experimental catatonia, proved to be so numerous that we finally considered the syndrome a general reaction-form of the central nervous system. The following table gives a brief outline of the numerous ways in which the catatonic syndrome can be elicited.

(A) CHEMICAL AND BIOCHEMICAL

1. Bulbocapnine. 2. Cannabis indica. 3. Mescaline. 4. Hormones. 5. Oxygen-lack (with gases or bilateral ligation of the carotid artery). 6. Urinary extracts. 7. Auto-intoxication (ligation of hepatic artery, Eck's fistula, ligation of the intestine). 8. Nicotine. 9. Idolaethylamine.

(B) ELECTRICAL

1. Leduc's current. 2. Faradic current. 3. Electric shock.

(C) DIFFERENT BRAIN LESIONS

Frontal, parietal and occipital cortex; maybe only in case of brain swelling.

(D) CENTRIFUGATION

(E) AUDIOGENIC STIMULATION

(F) "ANIMAL HYPNOSIS" (only catalepsy)

The purpose of another group of experiments especially carried out with the collaboration of Geesink, Nieuwenhuyzen and Kok[2,5] in our laboratory, had to do with the following consideration: Mescaline, bulbocapnine, surgical intervention in the brain, electrical stimuli to the brain etc., are all produced and procedures alien to the human body. Would it be possible to produce circumstances in the body in which toxins might be produced by the body itself? Thus, a great number of experiments were done in order to alter metabolic functions (Experimental Auto-Intoxication).

*Fig. 1.* A cat in a cataleptic position between two chairs. The animal is able to hold itself (active immobility, in contrast to paralysis), but does not move. Intramuscular injection of 30 mg. of bulbocapnine hydrochloride per Kg. cat.

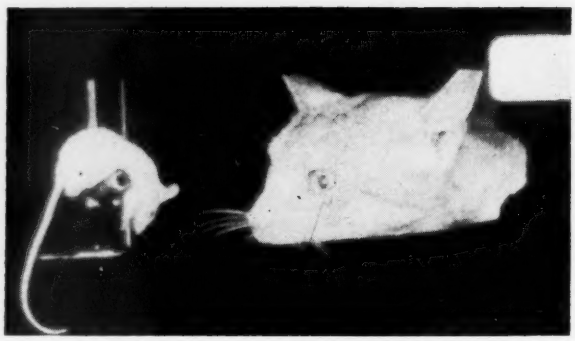

*Fig. 2.* Cat and mouse facing each other without moving, both under the influence of bulbocapnine hydrochloride.

Removal of kidneys, spleen, several glands of internal secretion, severing of their blood supply did not produce any catatonic symptoms in animals.[5] Only if the metabolism was changed through intestine or liver, catatonic phenomena occurred in the experimental animal. A few examples will illustrate this.

1. Artificial ileus with closure in two places of the small intestine of the dog produced experimental catatonia in four out of twelve cases.[2,5]

2. Experimental Catatonia after Ligation of the Hepatic Artery in Cats. Experimental lesion of the liver function was produced by ligation of the hepatic artery proper or its two branches as close to the liver as possible.[2,6] Of twenty-four cats, sixteen showed positive catatonic signs, sometimes for a short time, but sometimes permanently. At times these catatonic symptoms were very marked. The postmortem examination showed vast necrosis of the liver.

3. Experimental Catatonia in Dogs with Partial Elimination of the Liver Function after Applying an Eck's fistula.[2,8] Elimination of the function of the liver by means of an Eck's fistula consists of making an anastomosis between the portal vein and the vena cava. Eck's fistula had been successfully applied in our institute to four dogs by Dr. Geesink,[7] who simplified the very difficult method of making the anastomosis between the two vessels. The results of the physiological observations of four of the dogs are as follows: two of the animals showed neurotoxic symptoms which can only be classified as experimental catatonia. The first of the two animals showed these symptoms very distinctly for about ten days; thereafter the motility became normal again. The second dog showed for about one month, off and on, spontaneous catatonia; during this period the susceptibility of bulbocapnine catatonia was enormously increased.

Conclusion: Experimental catatonia is a general reaction-form of the central nervous system. It seems there is no specificity as to etiology, with one exception: In the realm of experimental alteration of metabolic function a definite specificity occurs since catatonic signs appear only after partial changes of the function of the intestine and the liver.

*Fig. 3.* The patient, J.W., under the influence of 200 mg. bulbocapnine hydrochloride intravenously. The arms are put in the air by the examiner. From time to time she is told she can lay the arms down, which was never done.

II. *The Production of Catatonic Stupor in Man:* (Preliminary Report.)

Bulbocapnine was first administered in man in 1924 by the author in collaboration with Schaltenbrand.[10,11,12] The latter took it first himself in dosages up to 350 mg.

Our idea was to determine whether or not the hypokinetic action of bulbocapnine, as demonstrated in animals, would have a diminishing effect on tremor and other adventitious movements in man. This proved to be the case.

Tremor of paralysis agitans was studied first under different circumstances of "rest" and "action" and later after the intramuscular injection or oral administration of 100 to 200 mg. of bulbocapnine hydrochloride. In a great majority of cases the tremor could be checked for period of about one hour's duration, or somewhat longer. The same proved to be true in certain cases of clonus and chorea. The action of bulbocapnine in other cases of paralysis agitans with a comparison of the action of other drugs was undertaken by the author and William Herman.[13] Thus, it was proven that the hypokinetic effect of bulbocapnine was not only limited to animals but also to human beings.

In none of the above cases were catatonic phenomena observed. Later, Henner[14] of Prague worked with a higher bulbocapnine dosage of 200 to 500 mg.

*Fig. 4.* The fingers are moved in different ways by the examiner. Flexibilitas cerea is shown that way.

in order to study the "Parkinsonian-cerebellar antagonism." He states he produced a "Parkinsonian syndrome which certainly was not complete since there was no tremor." I concluded at that time that he mistook catatonia for Parkinsonism. The first to administer intravenous injections of bulbocapnine (in dosages of 100 mg. and more) was De Giacomo.[15,16] States comparable with clinical and experimental catalepsy and sleep were described lasting from 10 to 30 minutes. Catalepsy was obtained in 25 per cent of his cases. The cataleptic phase was often preceded by somnolence. Although a temporary rise of blood pressure was mentioned, the patients did not suffer any harmful sequela.

The present experiments with intravenous injection of bulbocapnine hydrochlorida done at Osawatomie State Hospital were done on two patients. One of them was J. W.

The patient is a 40-year old, colored woman, who, after a hectic history in which occurred the fact that her four children died in a fire, started acting peculiar in 1947. The patient says people have shot gas at her several times but that it does not bother her. She thinks she is a member of the Kansas City Police force. She thinks her husband is trying to kill her. She believes various other people and herself can throw their voices and talk together. The patient says she talks with President Truman by means of voice throwing and he tells her various things such as that she ought to travel. She believes Joe Louis is in love with her and that she often talks with him also.

The patient is diagnosed at present as Schizophrenic Reaction, Paranoid Type, with borderline intelligence. She never showed catatonic hypokinesis. She has had insulin shock therapy and also a course of anti-luetic treatment; her spinal fluid has always been normal. A transorbital lobotomy was performed December 21, 1951.

In our tests we first started injecting intravenously 50 mg. of bulbocapnine hydrochloride. After each injection an electrocardiogram was taken* as a safety procedure. Three times, 50 mg. of bulbo-

*Fig. 5.* The arms and fingers still remain in the imposed position.

*We are indebted to Dr. E. Grey Dimond, Professor of Medicine at Kansas University Medical School, for his advice in making electrocardiograms during the injections as a safety procedure. He also read the E.C.G's.

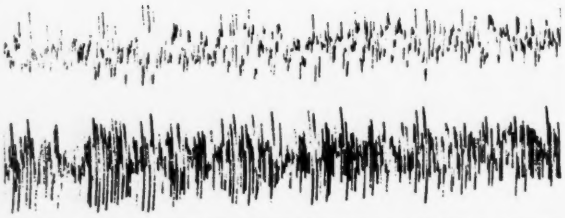

*Fig. 6.* Electromyograms during catatonic stupor induced by 200 mg. bulbocapnine hydrochloride in patient, J.W., muscles at rest.

capnine hydrochloride were given and only drowsiness, hypokinesis and sleep were noted. Her blood pressure remained 124/90 and her electrocardiogram was normal throughout the experiment except for one moment in the 3rd lead, probably due to misplacement of an electrode. This was February 10, 1955.

Our next experiment was taken February 17, 1955. The following shows a record taken during the experiment:

10:05 A.M.: Intravenous injection of 150 mg. bulbocapnine hydrochloride.
10:07 A.M.: Getting drowsy.
10:20 A.M.: Feels "kind of sleepy." Can get up, walks normally. Rotation test negative.** Right arm when stretched upward remains in that position about ten minutes.
10:30 A.M.: E.C.G.: Voltage is somewhat lower. The patient states she feels "better," less sleepy. Blood pressure: 120/75.
10:35 A.M.: Right arm flexed and up (a position induced by the examiner), remaining in that position. Also left with hand and fingers flexed down, after examiner puts them in this position.
10:40 A.M.: 50 mg. bulbocapnine are added.
10:45 A.M.: Patient is stuporous; mute and with eyes closed. Respiration: 18. Pulse: 68. Arm remains up when put in this position while patient looks as though she were asleep. She is told she can put the arm down, but only reacts with a faint smile without opening the eyes. E.C.G.: normal. Blood pressure: 115/75.
11:00 A.M.: 50 more mg. of bulbocapnine.
11:05 A.M.: Arm kept up straight when brought in that position.
11:12 A.M.: Stuporous and keeping up induced positions of arms, hands, and fingers; pulse and respiration as before. E.C.G.: normal.
11:30 A.M.: The patient opens her eyes. Can easily be induced to leave the bed. Rotation test negative. No more catalepsy.

February 18, 1955. The patient is normal again as far as psychomotor activity is concerned. She feels "better than before" and thanks the examiner profusely for his "therapy." Pulse and temperature are normal. No cataleptic signs can be evoked. When one of the arms is put up in the air, the patient moves it down almost immediately.

**This test was described by the author[2] as follows: Take the patient by the shoulder and rotate him along a vertical axis. In pronounced catalepsy the body acts like a piece of rubber and the feet move, only passively following the body. A normal or less deeply cataleptic person reacts with the feet actively moving to follow the torsion of the body.

*Cataleptic stupor appeared after 150 mg. of bulbocapnine hydrochloride intravenously. The dose was gradually increased to 250 mg. The E.C.G. remained normal. The catatonic stupor remained from 10:05 to 11:30.*

At first we thought we were dealing with "cataleptic sleep"; however, at 10:45 the patient reacted definitely with a smile upon being spoken to. At other moments she did not react at all when spoken to. She never opened her eyes and remained mute throughout the catatonic stage.

A control experiment with a sleeping patient showed that it was not possible to produce any catalepsy during real sleep. An arm, of a sleeping patient, elevated by the examiner dropped down immediately.

The protocol of the next experiment is as follows: In this case an electro-encephalogram and an electromyogram were taken during the course of the experiment.

9:25 A.M.: 200 mg. of bulbocapnine hydrochloride are injected intravenously.
9:30 A.M.: Some catalepsy is apparent.
9:35 A.M.: Another 50 mg. bulbocapnine are injected. The outward appearance of the patient is as though she were asleep; if spoken to, she did not answer but one moment just smiled. E.E.G. showed muscle potentials all over. Patient seems stuporous and catalepsy can be shown very easily in arms, hands and fingers; E.E.G. shows muscular spindles especially in the parietal lead.
9:40 A.M.: Electrodes are fixed on two places on the biceps and on two places on the triceps muscles. Strong muscular activity is registered in both regions when the arm is at rest.
9:45 A.M.: The arm is raised by the examiner and remains up; one moment a slow tremor is visible in the biceps muscle. The patient is still stuporous. Muscle potentials are visible from the two arm leads. (In flexors and extensors at the same time.)
9:50 A.M.: The patient was apparently sleeping. E.E.G. showed symmetrical sleep spindles. This condition lasted approximately ten minutes. Still muscle activity in both leads in the arm.
9:58 A.M.: Muscle tension in head leads reappeared.

### *Discussion*

Of particular interest, is the variety of methods of producing catatonia in animals and man. Apparently acetylcholine and its esterase are involved in this mechanism and trauma in either hypothalamus, thalamus or brain stem is capable of producing this clinical state. The need, however, for cortex in both hemispheres in producing this state substantiates the growing indication that very little if any of the brain acts independently. The combination of trauma and acetylcholine action has been very nicely demonstrated by McCulloch who, in working with cats, found that a recovering catatonic state due to coagulation of both ventro-medial nuclei of the hypothalamus was made worse on intraventricular injection of acetylcholine, while cholinesterase produced transient remissions in this dis-

ability. McCulloch's normal cats on similar doses of acetylcholine were not catatonic but were rather agitated and hallucinated with what sounded to me like the rage reaction of Cannon. Apparently in these animals there was predominantly an irritation of the hypothalamus rather than the more extensive dysfunction, catatonia, when this area had been previously traumatized.

I have had the opportunity of observing a young woman in a classical catatonic state, posturing, negativistic, hypersalivating etc., who died some 12 hours after my examination and was found to have a bilateral thrombosis of the internal cerebral veins and great vein of Galen. Some twenty years ago, while experimenting on the action of methylglyoxal injected into the 4th ventricle of the rabbit, Franks and I observed a classical catatonic state.

It would be of interest to know what effect lesions in the reticular substance would have on the production of catatonia by such drugs as bulbocapnine in view of the function of the reticular formations in respect to consciousness. We have been able to produce an apathetic state in the monkey by lesions in the reticular substance at about the level of the lateral geniculate body.

I believe that we have in these various methods of producing what appears to be a classical psychiatric clinical state, a method of investigation that will bring us closer to the scientific understanding of psychiatric states which at the present time are very confused and muddled. We are coming to appreciate that such a state as catatonia is the result of not a single lesion but rather the product of dysfunctions in various areas in the central nervous system and requires the presence of practically the intact central nervous system for this clinical entity.

The patient after intravenous injection of 150-200 mg. of bulbocapnine hydrochloride apparently showed a complete picture of catatonic stupor, including mutism and catalepsy. It was clear that she was not really asleep at 9:35, but only mute with closed eyes and she reacted, when spoken to, with a smile. Later, however, sleep spindles appeared in the E.E.G. for about ten minutes. Stupor and sleep may be related.

The electromyogram shows muscular activity in a flexor and extensor muscle of the arm at rest and during a cataleptic position. We are dealing, as in the animal experiment,[2] with active immobility. Muscular activity was also registered in the scalp muscles.

A second patient, who the day preceding the injection of bulbocapnine showed spontaneously a catalepsy comparable to the one induced in the first patient, did not display any catalepsy the next day, neither before nor after an injection of 150 mg. bulbocapnine hydrochloride.

*Summary*

A survey is given of work on experimental catatonia in animals which was started in 1921, which led to the description of experimental catatonia in animals by de Jong and Baruk. Later, the author found so many ways of eliciting experimental catatonia that he coined it a "general reaction form of the central nervous system."

This year experiments in man show that catatonic stupor can be produced temporarily by intravenous injection of bulbocapnine hydrochloride.

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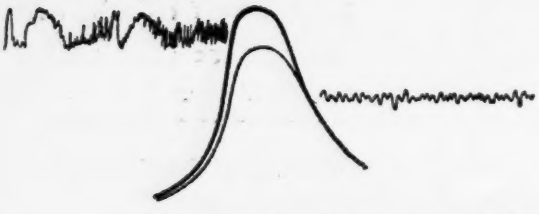

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